A CLINICAL STUDY OF HORMONE RECEPTOR STATUS IN CARCINOMA BREAST

DISSERTATION SUBMITTED TO

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI

in partial fulfilment of

the requirements for the degree of

MASTER OF SURGERY

In

GENERAL SURGERY

DEPARTMENT OF GENERAL SURGERY

TIRUNELVELI MEDICAL COLLEGE

TIRUNELVELI

APRIL-2016

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This is to certify that the dissertation entitled "**CLINICAL STUDY OF HORMONE RECEPTOR STATUS IN CARCINOMA BREAST**" is a bonafide research work done by **DR. KARTHIK**, Post Graduate M.S student in Department of Genereal Surgery, Tirunelveli medical college & Hospital, Tirunelveli, in fulfilment of the requirement for the degree of Master of Surgery in General Surgery.

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DESIGNATION OF PRINCIPAL INVESTIGATOR: Post Graduate in MS General Surgery
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1.	TIREC Application Form	☑
2.	Study Protocol	☑
3.	Department Research Committee Approval	☑
4.	Patient Information Document and Consent Form in English and Vernacular Language	☑
5.	Investigator's Brochure	☐
6.	Proposed Methods for Patient Accrual Proposed	☑
7.	Curriculum Vitae of the Principal Investigator	☑
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9.	Investigator's Agreement with Sponsor	☐
10.	Investigator's Undertaking	☑
11.	DCGI/DGFT approval	☐
12.	Clinical Trial Agreement (CTA)	☐
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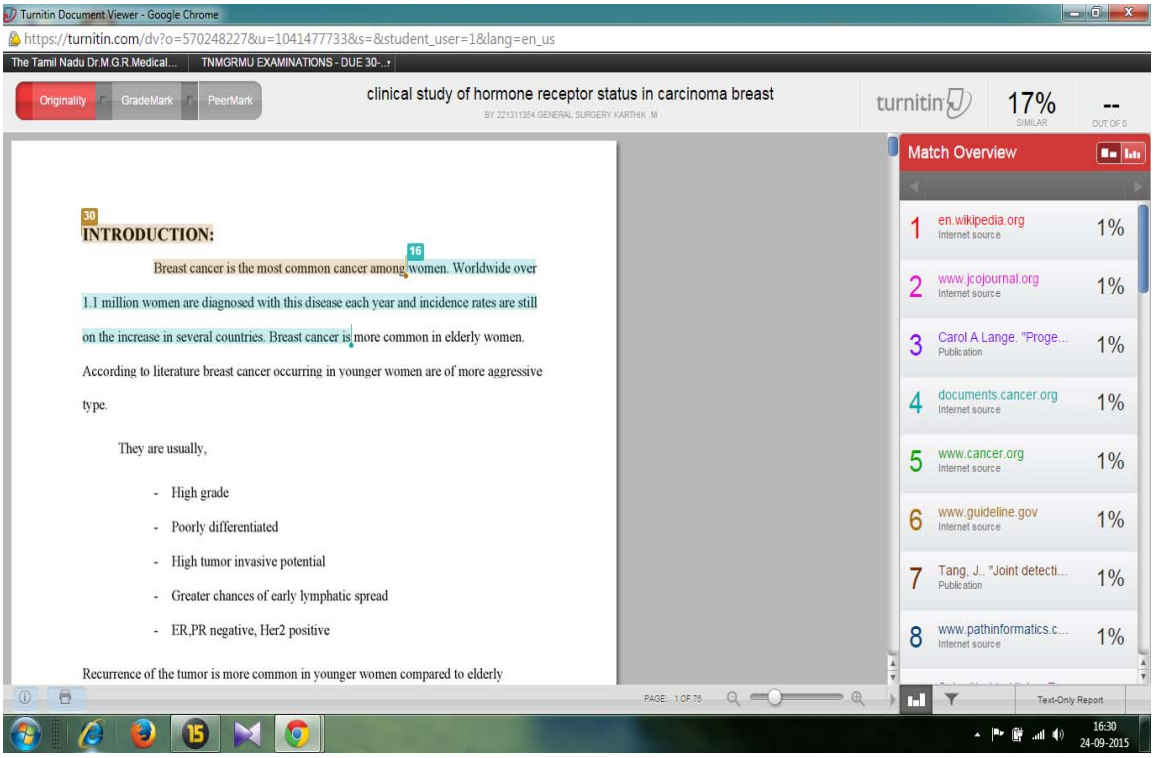
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INTRODUCTION:
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Breast cancer is the most common cancer among women. Worldwide over 1.1 million women are diagnosed with this disease each year and incidence rates are still on the increase in several countries. Breast cancer is more common in elderly women. According to literature breast cancer occurring in younger women are of more aggressive type.
They are usually,
- High grade
- Poorly differentiated
- High tumor invasive potential
- Greater chances of early lymphatic spread
- ER,PR negative, Her2 positive
Recurrence of the tumor is more common in younger women compared to elderly
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DECLARATION BY THE CANDIDATE

I hereby declare that the dissertation entitled "**CLINICAL STUDY OF HORMONE RECEPTOR STATUS IN CARCINOMA BREAS**T" is a bonafide and genuine research work carried out by me under the guidance of **Dr.R.MAHESWARI M.S.** Professor, Department of General Surgery, Tirunelveli Medical College, Tirunelveli.

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ABSTRACT

Aim of the study:

The aim of the study is to assess the incidence of hormone receptor positivity in females with carcinoma breast in relation to its clinical and pathological characteristics and thereby predicting the tumor response to endocrine therapy and to formulate the adjuvant treatment modality.

Materials and Methods:

The study sample included 75 female patients with carcinoma breast. They were selected from the general surgical wards of Tirunelveli medical college hospital and thye study was done for a period of 18 months.

Biopsy samples (either Trucut biopsy or postop mastectomy specimes) were sent to pathology lab where they were processed and analysed for the histological subtype of the tumor, its pathological grading and the clearance of resected margins of the tumor.

Hormonal receptor assay was done using Immunohistochemistry technique in our college pathology department and results were interpreted.

Inclusion criteria:

1. Clinically diagnosed breast malignancy in females of all age groups
2. Age of patient, tumor size, histological subtype and grading of the tumor
3. Trucut biopsy and mastectomy specimens

Exclusion criteria:

1. Patients already treated for contralateral breast carcinoma
2. Male breast carcinoma

Results:

In my study a total of 75 female patients with breast cancer in my institute were studied. the incidence of ER, PR, Her2 neu receptors among them correlating with age, tumor size, histological type and the pathological grading was evaluated. 52 patients (69.33%) were positive for estrogen receptor and 23 (30.66%) were negative. 39 patients (52%) were progesterone receptor positive and 36 (48%) were progesterone receptor negative. 28 (37.33%) patients had Her2 receptor positive and 47 (62.66%) were negative. Most of the tumors in women above45 years of age were hormone receptor positive. In women younger than 45 years both positive and negative were nearly equal.

Conclusion:

These results were comparable with the previous studies and thus reinforce the usefulness of estimation of the receptor status for treatment purpose in breast carcinoma. The patients with hormone receptor positivity in my study received endocrine therapy with tamoxifen.

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Introduction

INTRODUCTION

Breast cancer is the most common cancer among women. Worldwide over 1.1 million women are diagnosed with this disease each year and incidence rates are still on the increase in several countries. Breast cancer is more common in elderly women. According to literature breast cancer occurring in younger women are of more aggressive type.

They are usually,

- High grade
- Poorly differentiated
- High tumor invasive potential
- Greater chances of early lymphatic spread
- ER,PR negative, Her2 positive

Recurrence of the tumor is more common in younger women compared to elderly women.

Clinically, in young age, breast tumors are of large size, with greater lymphatic spread.

The most important prognostic factor is lymph node status(N) and next to it is the tumor size(T).

The final outcome in breast cancer management depends upon the initial stage of the tumor at diagnosis and associated prognostic factors such as status of the lymph nodes, size of the tumor and grading of the tumor.

Therefore it is essential to find the markers that have predictive and prognostic values. It predicts the chances of recurrence of cancer and also identifies which patients do and which do not benefit from adjuvant treatment.

So, patients with low-risk are avoided of unnecessary adjuvant treatment. And also the patients with high risk could be identified and given appropriate, early and aggressive treatment.

Estrogen and progesterone receptors (ER, PR) and more recently, HER-2/neu have with increasing importance influenced the management of the malignancy. Immunohistochemical (IHC) detection has become essential to many malignancies and plays a key role in tumor diagnosis, treatment and prognostic assessment.

In this study, we studied 75 cases of breast cancer patients, to detect the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2), by IHC and analyzed the associations between these indicators and the clinico- pathological characteristics.

Aim of the Study

AIM OF STUDY

To assess the incidence of hormone receptor positivity in females with carcinoma breast.

OBJECTIVES OF THE STUDY:

1. To identify hormonal receptor status in female patients with breast malignancies
2. To predict the tumor response to endocrine therapy
3. To compare hormonal receptor status with clinicopathological grading of the tumor
4. To formulate the adjuvant treatment modality

Methodology

MATERIALS AND METHODS

A study of cases of carcinoma breast in females were done. Sample included 75 patients. Patients for clinical study were selected from the general surgical wards of Tirunelveli medical college hospital for a period of 18 months. The study subjects were selected when they presented with the following inclusion and exclusion criteria.

Inclusion criteria:

1. Clinically diagnosed breast malignancy in females of all age groups
2. Age of patient, tumor size, histological subtype and grading of the tumor
3. Trucut biopsy and mastectomy specimens

Exclusion criteria:

1. Patients already treated for contralateral breast carcinoma
2. Male breast carcinoma

Method used:

Biopsy samples (either Trucut biopsy or post-op mastectomy specimens) were sent to pathology lab where they were processed and analysed for the histological subtype of the tumor, its pathological grading and the clearance of resected margins of the tumor.

Hormonal receptor assay was done using Immunohistochemistry technique in our college pathology department and results were interpreted.

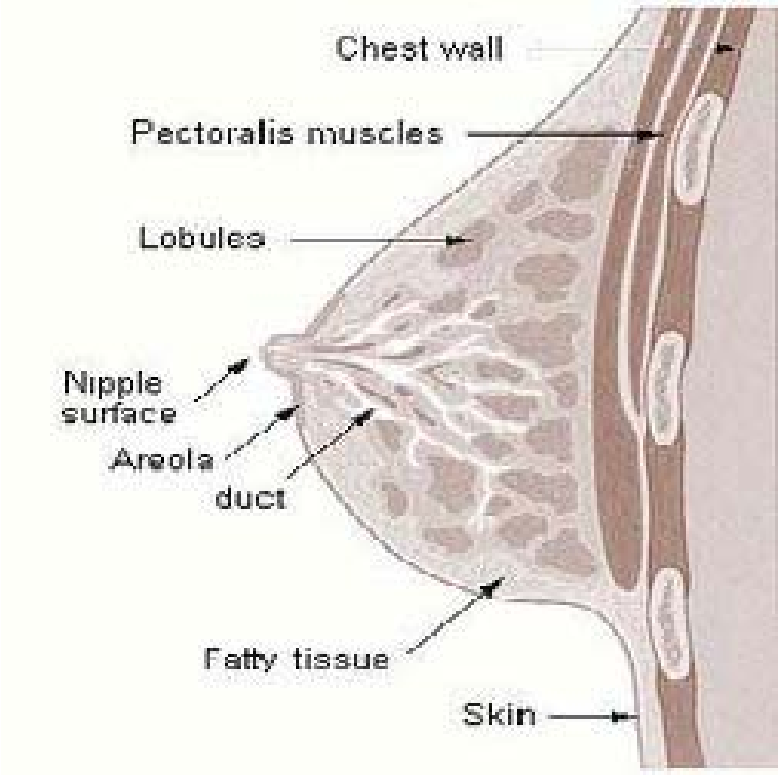
Review of Literature

REVIEW OF LITERATURE

Carcinoma breast is more common in developed, western countries. It is the second most common cancer in females. Incidence is 19-34%. Median age of onset is 47 years. Malignancy in one breast increases the risk of developing malignancy in the other breast by 3 – 4 times. It can be familial in 2- 5% patients.

Anatomy of the breast:

1. The breast is a modified sweat gland derived from the ectodermal milk lines bilaterally in 7th week of intrauterine life.
2. It is an accessory reproductive organ.



Situation:

The breast lies in the superficial to the fascia.

Axillary tail of Spence- extension of the breast that passes through the foramen of Langer and therefore this part of breast is deep to the fascia.

Significance: 1. Proximity to anterior group of axillary nodes. So malignancy in tail of breast may be mistaken for lymph node enlargement.

Extent:

Vertically- Second to the sixth rib

Horizontally- mid-axillary line to the lateral border of the sternum

Deep relations:

1. Muscles deep to breast-

   pectoralis major

   serrartus anterior

   external oblique of the abdomen.

2. Separated from deep fascia by loose areolar tissue.

Structure of the breast: Breast is a glandular tissue embedded in fibrofatty stroma.

The skin: Nipple - A conical projection present at the level of fourth intercostal space. 15 to 20 lactiferous ducts pierce the nipple. It contains circular and longitudinal smooth muscle fibres that makes the nipple to contract.

Areola- skin surrounding the nipple base and is pigmented

The parenchyma:

- -Made of glandular tissue containing 15 to 20 lobes.
- -Each lobe is made up of group of alveoli and it is drained by lactiferous duct.
- -Each duct has a dilatation at its termination - lactiferous sinus beneath the nipple.
- -Primary secretory unit - group of alveoli draining into duct.
- -Myoepithelium surrounds only the ducts. It is a single layer of epithelial cells. It does not line the lobules.
- -They are contractile and aids the transport of secretion along the duct.

The stroma:

- fibrous stroma- suspensory ligaments of cooper
- fatty stroma- the major part of the gland.

Blood supply of the breast:

The breast is highly vascular.

1. Medially- Internal thoracic artery- a branch of subclavian artery
2. Laterally- lateral thoracic, superior thoracic and acromiothoracic branches of the axillary artery
3. Posterior intercostals arteries branches

The veins follow the arteries.

Superficial veins- drain into the internal thoracic vein.

The deep veins- to the internal thoracic, axillary and posterior intercostals veins.

The communication of posterior intercostals veins with the Batson's vertebral venous plexus is the basis of spread of breast malignancy to vertebra and skull base

Nerve supply:

Anterior and lateral cutaneous branches of the 4^{th} to 6^{th} intercostals nerves.

Sensory fibres- to skin

Autonomic fibres- to blood vessels and smooth muscle.

Lymphatic drainage of breast:

Lymph from the breast drains into the following nodes.

1. Axillary nodes- defined by pectoralis minor muscle
    - Level 1 – lateral
    - Level 2 – posterior
    - Level 3 – medial
        a. Anterior or pectoral group
        b. Posterior or subscapular group } level 1
        c. Lateral or humeral group

d. Central group - level 2

e. Apical group - level 3

2. Internal mammary (parasternal nodes)- situated along internal thoracic vessels

3. Interpectoral or rotters nodes- between pectoralis major and minor

4. Some also reaches

- the supraclavicular nodes

- the cephalic(deltopectoral) nodes,

- the posterior intercostals nodes

- subdiaphragmatic and subperitoneal lymph plexuses.

5. Few lymphatic pierce the pectoral fascia & enter the chest

The lymphatics pass radially to the surrounding lymph nodes. The deep lymphatics drain the parenchyma of breast. They also drain the nipple and areola.

1. About 75% of the lymph-into the axillary nodes

20% into the internal mammary nodes

5% into the posterior intercostal nodes.

Among the axillary nodes, they mostly drain- into the anterior group partly into the posterior and apical group.

2. The internal mammary nodes drain the lymph not only from the inner half of the breast but from the outer half as well.

3. A plexus of lymph vessels- subareolar plexus of Sappey, is present deep to the areola.
4. The lymphatics from the deeper surface of the breast pass through the pectoralis major muscle and the clavipectoral fascia to reach the apical nodes and also to the internal mammary nodes.
5. Lymphatics from the lower and inner quadrants of the breast

crosses the costal margin and pierces the anterior abdominal wall through the upper part of linea alba.

communicate with the subdiaphragmatic and subperitoneal lymph plexuses

Aetiological factors:

1.Geography :

More common in the Western World

2.Age:

Rare below 20 years of age.

The incidence is more common after 40 years of age and keeps rising

3.Gender:

Females- most common

<0.5% of patients- men

4.Genetic:

-Women with a family history of breast cancer

- About 5% of breast cancers are related to specific mutations.

5. Breast cancer syndrome:

i) Li-Fraumeni syndrome

P53 gene mutation

Autosomal dominant mutation

ii) Cowden's disease

Multiple hamartoma syndrome

Facial trichilemmoma, papilloma, bilateral breast cancer

iii) Ataxia telangiectasia

Hemangioma breast cancer

6.Chromosomal Abnormalities:

i) BRCA one gene mutation – Chromosome 17q

Poorly differentiated

Invasive ductal type

Hormone receptor negative

Associated with ovarian, prostate and colon cancers

ii) BRCA-2 gene mutation – Chromosome 13 q

Well differentiated

Invasive ductal carcinomas

Express hormone receptors

Associated with ovarian, colon, prostate, pancreas, gallbladder, bile duct, stomach cancers and melanoma

iii) HER-2 mutation (rbB2, transmembrane growth factor)

Invasive breast cancer ; upto 80% ductal carcinoma

Poor prognosis

iv) P 53 mutation

Associated with poor prognosis

Resistance to chemotherapy

7. Diet:

There is a causal association between breast cancer risk and diets low in phytooestrogens.

Alcohol intake- increased risk of developing breast cancer.

8. Endocrine:

- Common in nulliparous women

- Protective factors-

  - breast feeding
  - first child at an early age
  - late menarche and early menopause.
    - In post menopausal age, it is more common among obese persons due to the conversion of steroids to estrogen in their body fat.
    - Exogenous hormones- such as oral contraceptive pill and HRT, their role is controversial. But the benefits of these treatments overcome the adverse effect of developing breast cancer
    - The relative risk (RR) is used to quantify the increase in the chances of developing breast cancer associated with the above risk factors.

RR 2.0- indicates that she has two times more risk of developing breast cancer than the general population

RR of 0.5- indicates 50% decrease in the risk.

Basic pathology behind carcinoma breast is explained by Koreman's hypothesis. Anovulatory cycles are more common when there is unopposed

estrogen with no progesterone that are usually present in early menarche and late menopause. Hyperprolactinemia is inhibited in early child birth.

Clinical features:

Carcinoma breast usually presents as

1. Painless hard Lump
2. Nipple retraction- invasion into lactiferous ducts
3. Nipple discharge
4. Dimpling or puckering of skin- cooper's ligament involvement.
5. Peau d'orange- due to obstruction of dermal lymphatics, opening of sebaceous glands and hair follicles get buried in the edema giving rise to the orange peel appearance.
6. Edema of the arm- occurs due to axillary dissection and radiotherapy to axilla. It can also occur due to infiltration of the axilla by the tumor causing the arm to swell due to blockage of both lymphatic and venous flow. It can be painful due to the involvement of brachial plexus.

Complication of the edema is infection and are at a higher risk. It requires vigorous treatment with antibiotics.

7. Cancer-en-cuirasse-

It occurs due to tumor infiltration of the chest skin and appears like a armour of coat.

It can occur in patients with-

-local recurrence after mastectomy

-irradiation to the chest wall.

Treatment- palliative

8. Lymphangiosarcoma- appears as multiple subcutaneous nodules in the limb.

Poor prognosis

Some respond to chemo or radiotherapy

Interscapulothoracic forequarter amputation is other option

STAGING EVALUATION:

` - examination of the patient clinically

- X ray of chest

- C.T scan of chest

- ultrasound abdomen

- bone scan if necessary

Staging of the tumor is essential to determine both the prognosis and treatment of the patient.

A patient with systemic metastasis, is likely to benefit from systemic chemotherapy to combat the metastasis than with surgery for the local disease.

Pathology:

Breast cancer may arise from the

- the duct system epithelium- most commonly

- the lobular system of breast.

It may be

- in situ

- invasive cancer

Insitu lesions are now more common due to the increased detection during screening programs.

The grading of the tumor according to the degree of differentiation of the tumor are:

- well differentiated
- moderately differentiated &
- poorly differentiated

The three factors used for the numerical grading system are,

- nuclear pleomorphism
- tubule formation
- mitotic rate

With the increase in the use of molecular markers, much more information about an individual tumor will be routinely reported, such as the likelihood of metastasis of tumor and the susceptibility of the tumor to treatment regimen.

Pathological classification:

INSITU		INVASIVE
Ductal	lobular	- infiltrating ductal
		- Invasive lobular
• Comedo		- Ductal/lobular
• Cribriform		- mucinous/ colloid
• Micropapillary		- tubular
• Papillary		- medullary
• Solid		- papillary

Nomenclature:

- Ductal carcinoma - most common variant
- lobular carcinoma - in15% of cases. Subtypes are
  - classical type- better prognosis
  - pleomorphic type
- mixed ductal and lobular

Rare variants:

- colloid type- abundant mucin production
- medullary type- sheets of large cells with lymphocytic reaction
- tubular type

Invasive lobular variant – they are usually bilateral and multifocal/ multicentric.

Inflammatory carcinoma:

- Inflammatory carcinoma is a highly aggressive cancer and rare variant.
- It presents as a painful, swollen breast, with erythema but no clinically palpable mass.
  - occlusion of the lymphatics in subdermis by the carcinoma cells.
- It mimics breast abscess.
- To confirm the diagnosis- biopsy- undifferentiated carcinoma cells.

- Treatment options - aggressive chemotherapy, radiotherapy with salvage surgery

In situ carcinoma :

- preinvasive cancer
- No epithelial basement membrane breach
- Now more common due to early mammographic screening.
- Types
- ductal (DCIS)
- lobular (LCIS)

Both are markers for the development of invasive cancer in the future

-DCIS classified by the Van Nuys system. It includes

- Age of patient
- type
- microcalcification +/-
- margin extent
- size

Patients with a high score – radiotherapy is required after excision

Low score - needs no further treatment after excision.

Paget's disease of the nipple:

- It is the superficial manifestation of an underlying breast malignancy.

- It appears as eczematous lesion of the nipple and areola
- The nipple gets finally destructed.
- Microscopically- large, ovoid cells with abundant, clear cytoplasm in the Malpighian layer of the epidermis.

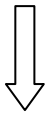
Pathogenesis of Carcinoma Breast:

Prolonged estrogen exposure

Genetic mutations

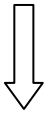
Environmental factors

Gender, age

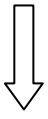


Mutations resulting in loss of p53, inhibition of apoptosis, cell cycle propogation

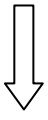
Dysplasia



Metaplasia



Insitu carcinoma



Invasive malignancy

Staging of carcinoma breast: TNM staging

T stage:

T1- tumor size <2cm

1a- 0.1- 0.5cm

1b-0.5- 1cm

1c- 1 -2 cm

T2- size 2- 5cm

T3- size >5cm

T4- any size with

4a- fixed to chest wall

4b- fixed to skin

4c- both 4a and 4b

4d- inflammatory carcinoma of breast

N stage:

N0- no nodes

N1- mobile ipsilateral axillary nodes

N2- N2a- ipsilateral axillary nodes fixed

N2b-ipsilateral internal mammary nodes without axillary nodes

N3-

N3a- ipsilateral infraclavicular nodes +/- axillary nodes

N3b-ipsilateral internal mammary and axillary nodes

N3c-ipsilateral supraclvicular nodes +/- axillary and internal mammary node

M stage:

M0- no metastasis

M1- distant metastasis

Prognosis of breast cancer:

The best indicators for prognosis are

- size of the tumor at presentation
- status of the nodal involvement
- invasive and metastatic potential.

Prognostic factors defined include

- grading of the tumor
- receptor status
- measures of proliferation of the tumor - S-phase fraction and thymidine labeling index
- analysis of growth factor
- measurement of oncogene or oncogene products

Role of estrogen in carcinoma breast:

Estrogens play a major role in promoting the proliferation of both the normal and the neoplastic breast epithelium. Its role as breast carcinogens has been recently confirmed by epidemiological studies.[5] Their carcinogenic effects are believed to be due to three different hypothesis:

1. Through their receptor-mediated hormonal activity it causes stimulation of cellular proliferation.
2. Through cytochrome P450-mediated metabolic activation it increases the mutation rates and thereby causes direct genotoxic effects
3. induction of aneuploidy.

How levels of estrogen are affected by lifestyle factors?

Diet:

Increase the risk of cancer by

- Directly increasing the estrogen amount in blood or
- indirectly by causing obesity.

Obesity increases the cancer risk in postmenopausal women.

Dietary phytoestrogens:

Phytoestrogens are estrogens found in plant foods.

A diet rich in phytoestrogens decreases the risk of breast cancer.

They are weaker estrogens that bind to estrogen receptors and inhibits the binding of human estrogens to the receptor, and thereby decreases the rate of division of breast cells.

The menstrual cycles in women taking diet rich in phytoestrogens are longer and fewer. All these factors results in decreased risk of breast cancer.

Body weight: Breast cancer risk increased by weight gain. In postmenopausal women, the ovaries stop producing estrogen and hence the primary source for estrogen in them is their body fat. Therefore women with higher levels of body fat in the postmenopausal period are expected to have a higher level of estrogens compared to a lean woman of their age. Trying to limit the increase in weight gain by eating healthy diet, and doing exercise reduce their risk of breast cancer .

Exercise: Women doing exercise regularly have lower estrogen levels, due to decrease in the body fat, thereby decreasing the breast cancer risk. Exercise may also increase the duration of menstrual cycles and results in decreased exposure to estrogen. So younger women are advised to do regular exercise.

Alcohol: Alcohol drinking increases the breast cancer risk, which is proportional to the amount of alcohol intake. Some theories suggest that estrogen levels increase due to alcohol consumption.

Birth control pills: Its association with breast cancer is controversial. It depends on the

- estrogen quantity in the pill

- the duration

Postmenopausal hormone treatment:

After menopause, estrogen production in the ovaries gets stopped. Estrogen loss increases the risk of blood vessel and heart disease, osteoporosis and symptoms of discomfort. To minimise these adverse effects estrogen replacement treatment has been used. But the adverse effect of therapy is the risk for endometrial carcinoma is increased. Due to this increased cancer risk, progesterone, which counteracts this risk, was also added to the treatment regimen. In women who have had hysterectomy, estrogen alone regimen can be used. Recent trials analysed that the postmenopausal treatment result in an increases the breast carcinoma risk but is unlikely to prevent the heart and blood vessel disease. So, many health associations have now recommended to stop the usage of hormone replacement treatment for health promotion and for prevention purpose of most diseases.

Role of progesterone in ca breast:

Progesterone is an steroid hormone from the ovary that is essential for the normal pubertal development of breast and also for the preparation for lactation and breastfeeding. Progesterone actions are mainly mediated by its high-affinity receptors, the progesterone receptors (PR)-A and -B isoforms. They are located in different tissues, such as the brain, where it controls reproductive behavior, and also located in the breast and reproductive organs. Progestins are usually used as contraceptive or in postmenopausal hormone replacement therapy, in which they are combined with estrogen inorder to counteract the estrogen-induced endometrial growth. The role of estrogen as a potent mitogen for breast is undoubted, and therefore the estrogen receptor inhibitors and the estrogen-producing enzymes inhibitors(aromatases) are effective first-line therapies for breast cancer. However, PR action in breast cancer is understudied and it remains controversial.

Role of her 2 neu:

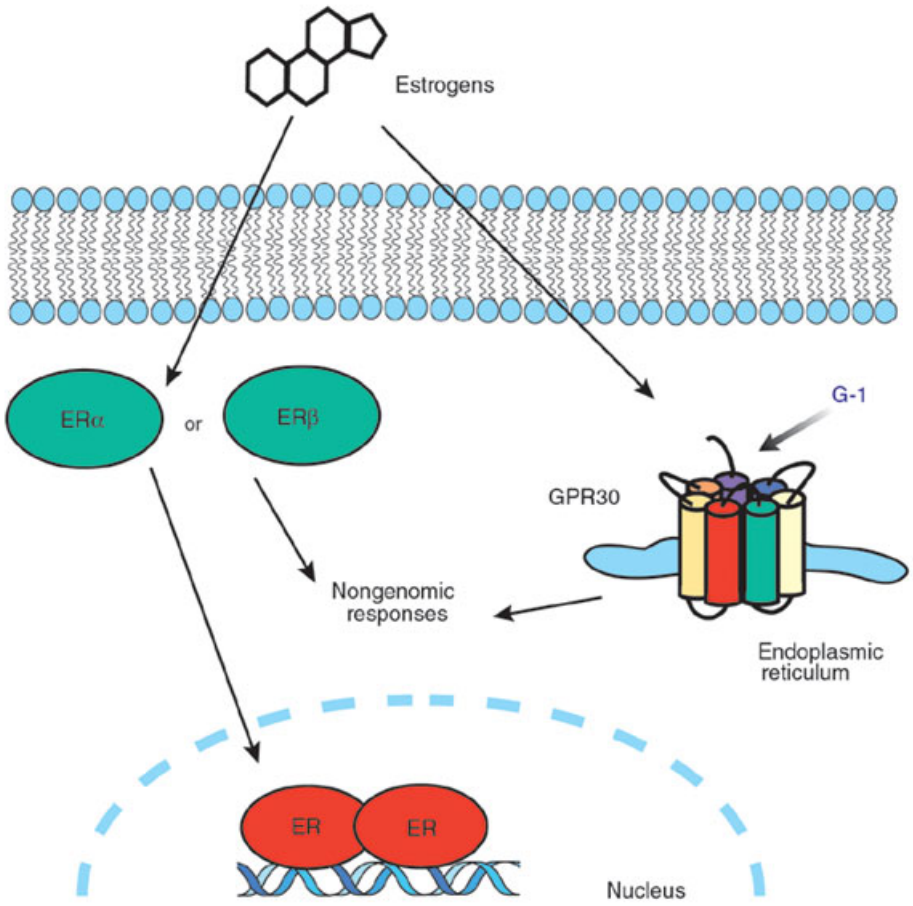
Over expression or gene amplification of the c-erbB-2/HER2/neu tyrosine kinase results in breast carcinoma of poor prognostic type. It manifests as increase in risk of metastasis, shorter disease-free intervals and refractory to treatment.

c-erbB-2 is activated by heterodimerization with other family members of the receptor family (EGFR, c-erbB-3, c-erbB-4).

Its activation augments the motility of the tumor cell, secretion of protease and tumor invasion, and modulates the checkpoint function of cell cycle,

apoptotic responses and DNA repair. It is expressed at low levels normally, and therefore the treatment modality is targeted against c-erbB2.

ESTROGEN RECEPTOR:

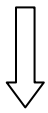


Estrogen receptors are proteins found inside cells. They are activated by the hormone estrogen (17β-estradiol). They occur as two different classes:

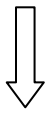
1. ER- an intracellular receptor belonging to nuclear hormone family
2. GPER (GPR30) –

   Here we discuss about the former ER type of receptor

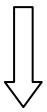
Once activated by estrogen



the ER translocates into nucleus



bind to the DNA



regulate activity of different genes.

It also has additional functions independent of binding of DNA.

There are two different forms of the estrogen receptor

- ER α
- ER β

Encoded by genes

ESR1 and ESR2 respectively.

Hormone-activated estrogen receptors form dimers.

- homodimers - ERα (αα) or ERβ (ββ)
- heterodimers- ERαβ (αβ)

Genetics:

The two forms of the estrogen receptor are encoded by

*ESR1*gene - on chromosome six

ESR2 gene - on chromosome fourteen

Distribution:

The ERα –

breast cancer cells

endometrium

ovarian stromal cells and

hypothalamus.

In males they are found in the efferent duct epithelium.

The *ERβ*- ovarian granulosa cells, heart, lungs, prostate, intestinal mucosa, endothelial cells, kidney, brain and bone.

The affinity differ with different ligands for binding to alpha and beta isoforms of the estrogen receptor

Selective estrogen receptor modulators (SERMs) selectively bind to either alpha or beta subtype of the receptor, which then leads to agonistic and antagonistic effects at selective sites.

The ratio of α- to β concentration is important in certain diseases.

The concept of SERMs is based on the ability to initiate the interactions of estrogen receptors with the proteins such as

- transcriptional coactivators
- transcriptional corepressors.

The ratio of coactivator to corepressor protein varies in different tissues. Therefore, the same ligand may be

- agonist at some tissue (where the coactivators predominate)
- antagonistic in other tissue (where the corepressors predominate).

Tamoxifen, is an antagonist in breast but an ER agonist in bone and is, therefore, used as a breast cancer treatment and also prevent osteoporosis. But it increases the risk of endometrial cancer due to its partial agonistic action at endometrium.

In around 70% of breast cancer cases, estrogen receptors are over-expressed and they are referred to as "ER-positive".

Why this causes tumorigenesis, is explained by two hypotheses:

Binding of estrogen to ER

stimulates the proliferation of mammary cells

increase in the cell division

DNA replication

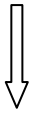
leading to mutations.

Estrogen metabolism

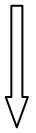
Produces genotoxic waste

mutations

Both these processes



Disruption of the cell cycle, apoptosis and DNA repair



Tumor formation

Other cancers associated with estrogen and its receptor are

-ovarian cancer

-endometrial cancer

-colon cancer

-prostate cancer.

The ERβ is the predominant ER in colon tissue. A loss of ERβ is associated with advanced colon cancer, and it is treated with ERβ-specific agonists.

To assess the sensitivity of the breast cancer lesions to hormonal treatment using tamoxifen and aromatase inhibitors, ER status is used.

However, some patients have *de novo* resistance to endocrine therapy.

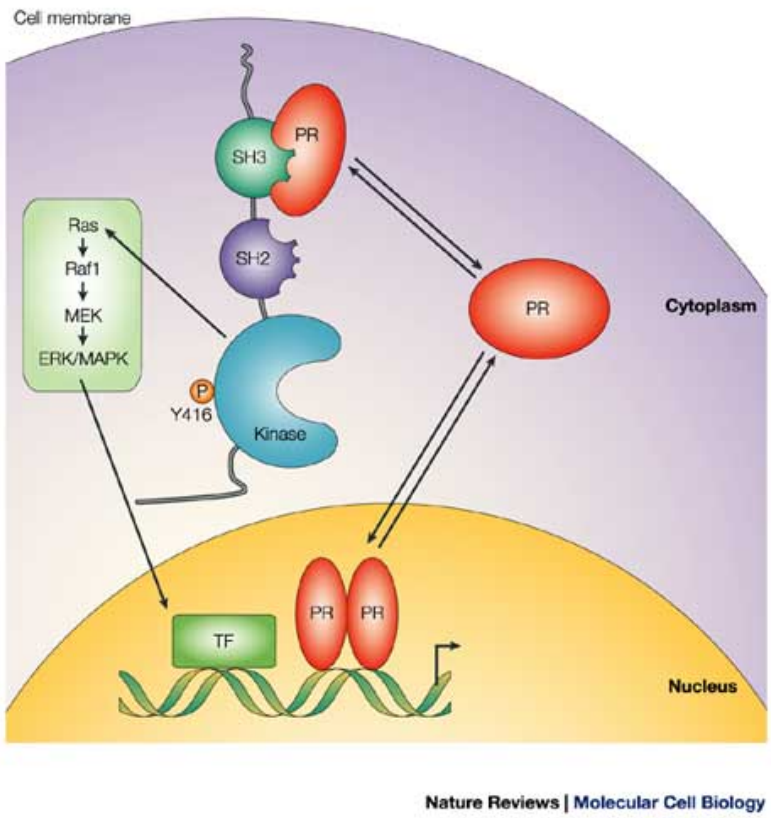
The ESR1 gene mutations are responsible for resistance.

Mutations in the ligand binding domain of *ESR1*

Constitutive estrogen-independent activity

Even in the absence of hormone stimulation tumor progression occurs

PROGESTERONE RECEPTOR:



The progesterone receptor (also known as NR3C3) is a protein found inside cells belonging to nuclear receptor subfamily. It is activated by progesterone, a steroid hormone .

PR is encoded by a single *PGR* gene on chromosome 11q22, It has two main forms

- PR A
- PR B

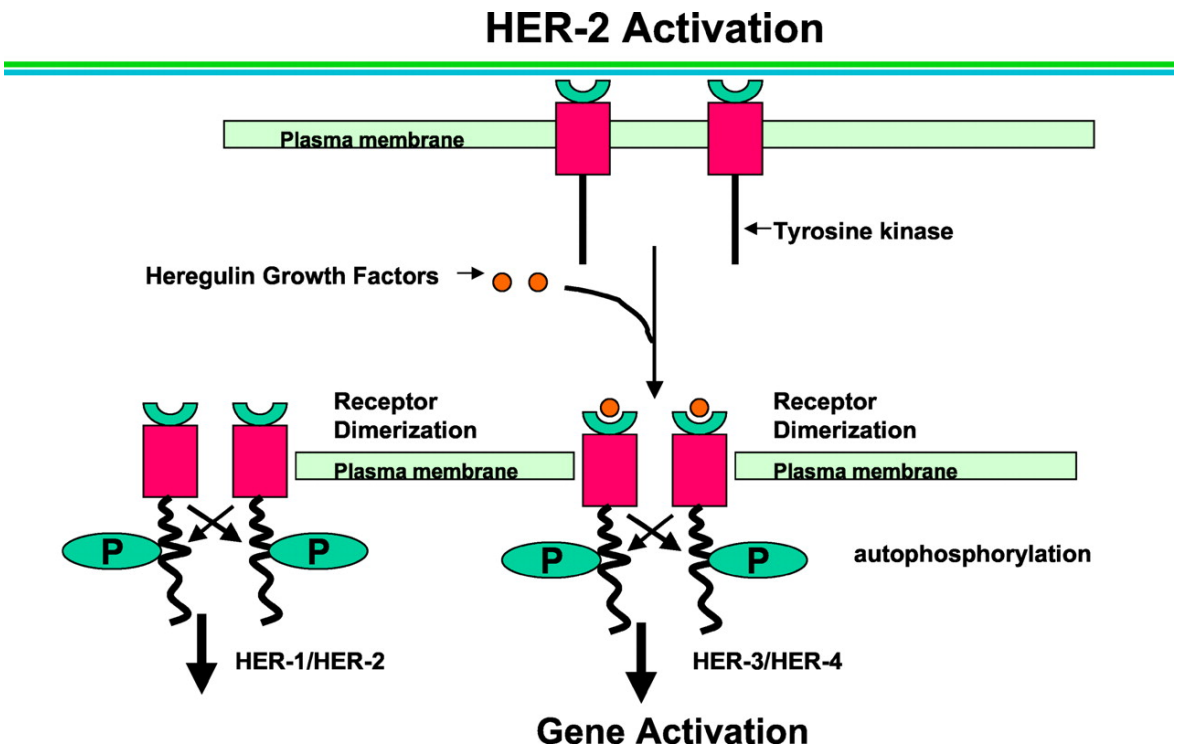
They differ in molecular weight.

Progesterone is essential to activate the progesterone receptors. When there is no binding hormone, the carboxyl terminal of the receptor inhibits transcription. Binding to the hormone induces structural change in the receptor that removes the inhibitory action of the carboxyl terminal. Progesterone antagonists prevent the structural reconfiguration of the receptor.

After progesterone interacts with its receptor, dimerization occurs and the Pg- PgR complex enters into the nucleus and then binds to DNA.

It leads to transcription and then formation of mRNA that is translated by the ribosomes to produce proteins.

Her 2 neu (erbb2) receptors:



ERBB2 a proto-oncogene

located at the human chromosome 17 (17q12).

The ErbB family consists of 4 membrane-bound receptor tyrosine kinases.

The other members of this family are

- epidermal growth factor receptor
- erbB-3
- erbB-4

All these four contain

intracellular domain

extracellular ligand binding domain

a transmembrane domain

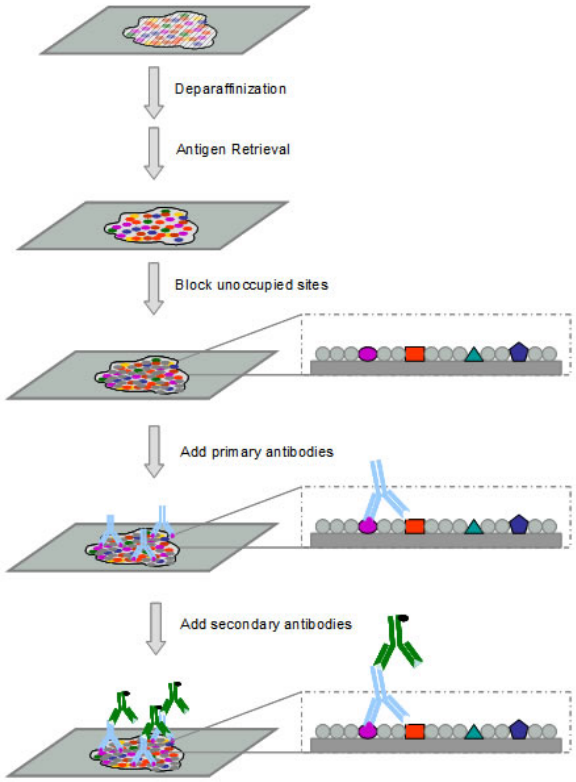
HER2 can dimerise with any of the other three receptors.

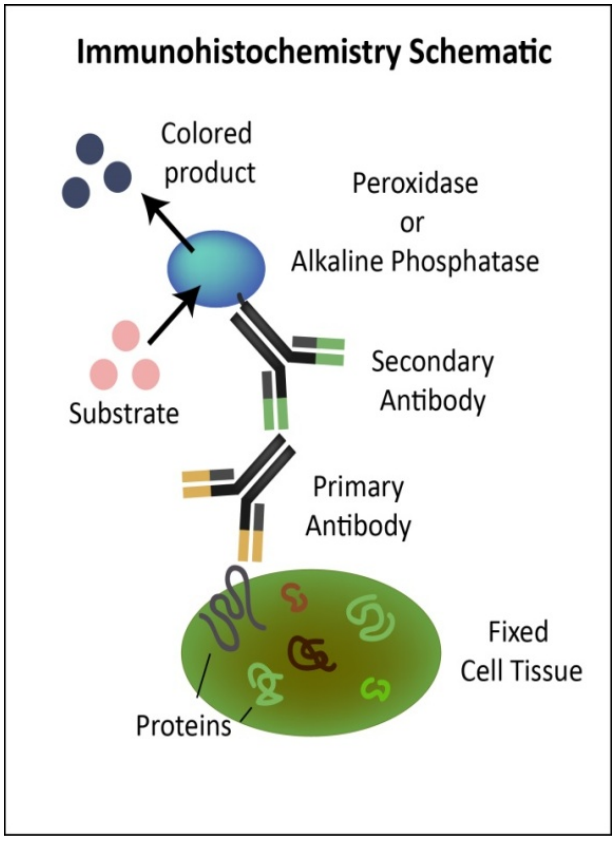
Dimerisation results in autophosphorylation of the tyrosine residues and initiates a variety of signaling pathways. It promotes cell proliferation and also opposes apoptosis.

ERBB2 gene amplification occurs in nearly 15-30% cancers. It results in increased recurrence of the disease and poor prognosis.

The estrogen, progesterone and the Her2 neu receptors are estimated from the tissue sample using immunohistochemistry technique.[6]

Immunohistochemistry:





Immunohistochemistry- By using the principle of antibodies binding specifically to antigens, detection of antigens in cells of a tissue.

The procedure was developed by Dr. Albert Coons in 1941.

In the diagnosis of abnormal cells, immunohistochemical staining is used. First the procedure involves proper collection of the tissue, then fixing it and then sectioning. Before sectioning it, to fix the tissue, Paraformaldehyde is used .

The sample may require additional steps such as deparaffinization and antigen retrieval, to render the availability of epitopes for antibody binding, and it involves treating with heat or protease.

The antibodies may also partially bind to nonspecific proteins sites. High background staining which masks the target antigen detection is caused by increased non-specific binding. In order to reduce the background staining, the samples are incubated with buffer. It blocks the reactive sites and thereby prevents the nonspecific binding of the primary or secondary antibodies to it.

The ***direct method-***

- single-step method
- a labeled antibody reacting directly with the antigen.
- Simple and rapid- as only one antibody used
- the sensitivity is lower due to low signal amplification. However, this is used less frequently than the muti-step indirect method.

In the ***indirect method-***

- Primary antibody (first layer) which is unlabelled, binds to the target antigen and a secondary antibody (second layer) reacting with primary antibody is used.
- More sensitive than direct test because of high signal amplification, which is due to the binding to each primary antibody by several secondary antibodies.

A second stain is often applied after immunohistochemical staining of the target antigen.

Dyes available for IHC include: hematoxylin, Hoechst stain and DAPI.

Molecular classification of breast cancer:

Research on patterns of gene expression has suggested newer ways to classify breast cancers based on the molecular gene expression.[1] Based on these, the breast carcinoma is categorized into four groups

- Luminal A
- Luminal B
- Her 2
- Basal like

Luminal A and luminal B types: estrogen receptor positive. These cancers express genes that are similar to normal cells.

- Luminal A cancers - low grade, grow slowly, best prognosis
- Luminal B cancers - grow faster, prognosis is not as good as Luminal A.

HER2 type: They have additional copies of the *HER2* gene.

- high-grade appearance
- tendency to grow more quickly
- worse prognosis
- treated with targeted therapies against HER2

Basal type:

- Usually triple-negative type.
- Estrogen and progesterone receptors deficient

  Normal HER2.
- Similar to the cells in the basal layers of breast ducts and glands in their gene pattern.
- BRCA1 gene mutations are mostly associated with this type of cancers.
- This cancer is also more common among younger women.
- They are high-grade cancers which grow quickly
- have a poor prognosis
- poor candidates for hormone therapy and anti-HER2 therapies
- Chemotherapy can be helpful.

IHC predicts the response of breast cancer to hormonal therapy better.

The Panel had recommended the cutoff to differentiate "positive" from "negative" cases as $\geq$ 1% ER-positive tumor cells.

It suggested

- Considering endocrine therapy in patients showing at least 1% ER-positive cells
- withholding the endocrine therapy if it is less than 1%.

These recommendations will also result in a slight increase in the application of endocrine therapy.

The stained tumor cells percentage provides predictive and prognostic information regarding the tumor.

Fewer studies have described “The relationship between hormone receptor levels and patient outcomes. Overall survival, disease-free survival, recurrence / relapse-free survival, 5-year survival, time to treatment failure, response to endocrine therapy, and time to recurrence were all positively associated with ER levels. Overall survival, time to treatment failure/progression, response to endocrine therapy, and time to recurrence were positively related to PR levels. These studies suggest that patients with higher hormone receptor levels will have a higher probability of positive outcomes and may influence oncologists' and patients’ treatment decisions.”

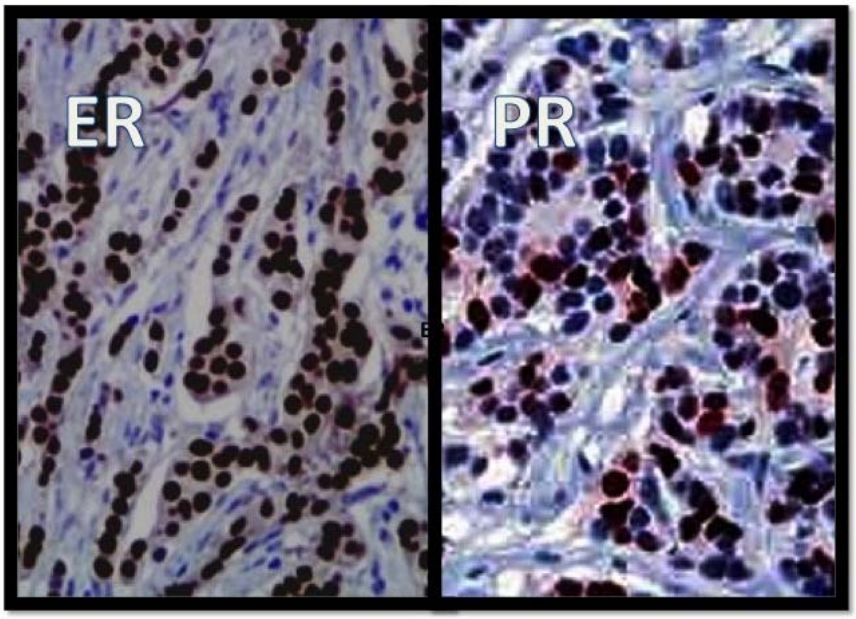
While some other literature suggest that “the predictive role of PR may not be as important clinically as ER, other studies have shown that PR status provides additional predictive value independent of ER values, especially among premenopausal women.”

Reporting the results of IHC:

Taking these into consideration, the Panel recommends that the ER and PR results shall be reported with

3 required result elements

2 optional result elements.



The three required elements are:

1. The percentage of tumor cells staining positive should be reported.

In the tissue section on the slide, all the areas containing tumor should be evaluated to arrive this percentage.

2. The staining intensity is measured and interpreted as
    - Weak
    - Moderate
    - Strong

It represents the average staining intensity of the positively stained tumor cells compared to positive controls.

3. A measure of assay quality over time is used to provide the intensity

The assay interpretation is based on:

- **Receptor positive:** (either ER or PR)

  Atleast 1% or greater of tumor cells positive for ER/PR

- **Receptor negative:**

If the tumor cells that do stain positive for ER or PR, are only less than 1% and of any intensity is considered negative and such patients do not benefit from endocrine therapy.

Negative should be considered only in the presence of extrinsic and intrinsic controls which stain appropriately.

If there are no intrinsic elements (normal breast epithelium) in the specimen and they show negative for receptor status, the assay should be repeated using another tumor specimen and then reported as uninterpretable.

- **Receptor uninterpretable:**

A result should be considered uninterpretable,

  - If the preanalytic specifications of the guideline for sample is not followed

- If the procedures used for processing the sample did not conform to the guideline specifications
- If the validated assay was not used for analyzing the specimen

Examples of conditions resulting in uninterpretable results are:

- Analyzing the samples that are fixed in alcohol, or using fixatives other than 10% neutral buffered formalin
- biopsies that are
  - fixed for shorter intervals less than 6 hours
  - or for longer intervals more than 72 hours
- fixation delayed more than 1 hour
- Using strong acids for prior decalcification of the samples
- Inappropriate staining of controls

If the result is uninterpretable, then the reason for it should be mentioned, and an alternative good sample should be suggested for retesting, if appropriate.

Two optional report elements that are recommended by the Panel, but are not required are:

1. A cautionary statement might be added to negative ER and PR, when the histopathology of the particular tumor is usually associated with ER-positive and PR-positive results.

   These tumors include tubular, mucinous and lobular histologic types or those tumors with Nottingham score of 1.

   The cautionary statement must indicate that though the patient's tumor is tested as ER negative, tumors almost always test positive with Nottingham score 1 or tumors having similar histological type.

2. Utilising the percentage and intensity measurements, the pathologist may provide a composite score such as the

   - H score
   - Allred score
   - Quick score

ER/PR scoring system and criteria:

SCORING SYSTEM	RECEPTOR STATUS	CRITERIA
0	Negative	0% nuclear staining
1+	Borderline	<10% nuclear staining
2+	Positive	10 - 75% nuclear staining
3+	Positive	>75% nuclear staining

Her2 neu scoring system and criteria:

SCORING SYSTEM	RECEPTOR STATUS	CRITERIA
0	Negative	No staining observed or membrane staining <10% of tumor cells
1+	Negative	A faint/ barely perceptible staining detected in >10% of tumor cells
2+	Weak positive	Weak to moderate complete membrane staining in >10% of tumor cells
3+	Positive	A strong complete membrane staining in >10% of tumor cells

Receptor status in different etiologies of Breast cancer:

Factors more consistently associated with increased risk of ER positive tumors are:

- Exposures related to reproduction
- Nulliparity and late child birth
- early menarche
- Postmenopausal obesity- possibly reflecting the increased synthesis of estrogen in adipose tissue and greater bioavailability of it.

The exogenous estrogen usage such as oral contraceptive pills or hormone replacement therapy, increasing the risk of hormone-sensitive tumors is not established.

Risk factors that do not differ by receptor status are:

- breast-feeding
- premenopausal obesity
- cigarette smoking
- alcohol consumption
- family history of breast cancer

Methods to assess hormone receptors:

1. Immunohistochemistry
2. Flow cytometry
3. Tissue microarray
4. FISH (Fluorescent insitu hybridization)

Advantages of immunohistochemistry :

- Easily available
- Inexpensive
- Rapid results
- Free of infectious agents so no human health risk
- Good cell morphology reservation

Limitations of immunohistochemistry:

1. molecular genetics could not be simultaneously assayed as in flow cytometry.
2. Fixatives used can affect some of the antibody binding sites making the interpretation difficult.
3. Standardisation is very difficult.
4. Difficult to quantitate.
5. Success depends on antibody.
6. Well trained pathologists are required.

Treatment for Breast cancer:

It’s a multimodality approach including

- Surgery
- Chemotherapy- adjuvant/ neoadjuvant
- Radiotherapy- to breast and axilla
- Hormonal therapy and anti Her2neu antibody

In this context, we discuss about the hormonal therapy pertaining to our topic, used in the management of breast cancer.

Hormonal therapy for the treatment of Breast Carcinoma:

Hormone therapy is a form of systemic therapy.

- As an adjuvant therapy- to minimize the cancer recurrence
- It can also be used as neoadjuvant treatment.
- It is also used for treating recurrent tumors
- Used for treating the metastatic spread of the tumors.

Source of estrogen:

- Before menopause- Ovaries
    - After menopause - the body's adipose tissue, where the adrenal androgens are converted to estrogen.

In patients having receptor-positive tumors, estrogen accelerates the tumor growth. In breast cancer, about two - thirds are hormone receptor-positive.

Most hormone therapy treatments for breast cancer act by

- Decreasing the amount of estrogen or
- by preventing the action of estrogen on its receptor in the tumor cells

This treatment is useful in patients positive for hormone receptors, but does not help the patients who are negative for hormone receptor.

Drugs that block estrogen action:

1. **Tamoxifen:**

The estrogen receptors in breast cancer cells are blocked

Estrogen binding to its receptors is prevented

- anti-estrogen effect in breast cells

  estrogen agonist effect in the uterus and bones.
- Due to this property of differential action, the name- selective estrogen receptor modulator or SERM.
  - In breast cancer positive for hormone receptor - tamoxifen for five to ten years as adjuvant treatment after surgery.
  - It decreases the recurrence of malignancy.
  - New breast carcinoma risk in the contralateral breast is reduced.

- For early stage breast lesion, this drug is mainly used before the women attain menopause.
- For women treated for ductal carcinoma in situ (DCIS), it reduces the chance of recurrence and its invasiveness.
- It inhibits the growth and cause shrinkage of tumors in women with tumor metastatis.

Side effects of SERM:

Common side effects:

1. Fatigue
2. vaginal dryness or discharge
3. hot flashes
4. mood swings.
5. "tumor flare"- in patients with metastasis to bones- causing pain in the muscles and bones.

Some of the serious and rare side effects are:

1. Increased risk of developing endometrial cancer and uterine sarcoma in postmenopausal women. a common presentation of these side effects are vaginal bleeding. But most uterine bleeding is not due to malignancy, and this symptom always needs immediate attention.

2. Coagulopathy. It usually occur as deep venous thrombosis in the legs, but can also sometimes cause pulmonary embolism due to dislodge or break in the clot. Symptoms are pain, erythema, or swelling in calf muscles, dyspnea, chest pain or hemoptysis.
3. Rarely, tamoxifen is associated with stroke in post-menopausal women which may present as severe headaches, confusion, or difficulty in speaking or moving.

Tamoxifen has different effects on the bones depending on a woman's menopausal status,

In pre-menopausal women- causes bone thinning

In post-menopausal women- it prevents osteoporosis.

The benefits outweigh the risks for almost all women taking these drugs.

Dosage- 10 mg twice daily for a period of 5 years

Toremifene: A SERM drug approved only to treat the metastatic breast cancer.

Fulvestrant:

- Estrogen receptor is blocked and then also temporarily eliminated.
- Not a SERM
- Estrogen antagonist action in all tissues in the body.
- Fulvestrant is used to treat advanced or metastatic breast cancer.
- It is administered as intramuscular injection in the gluteal region.
- first month- given in the dose of 2 weeks apart.

- Then once in a month.
- Adverse effects - night sweats, hot flashes, fatigue and osteoporosis
- Use- for treating advanced breast cancer in the post-menopausal women.
- It can sometimes be suggested “off-label” in women before attaining menopause, along with LHRH agonist to turn off the ovaries.

Raloxifene:

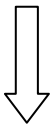
It is also a SERM which has antiestrogenic action on both breast and endometrium and estrogen agonist in bones. So it has the advantage of no increased risk in endometrial cancer and also prevents osteoporosis.

Dosage- 60 mg tablet once daily

Treatments causing decrease in the amount of estrogen:

Aromatase inhibitors (AIs):

Adrenal androgens



Aromatase × (aromatase inhibitors)

Estrogen

- In post-menopausal women, these drugs prevent the production of estrogen and breast carcinoma in early and late stages can be treated using it.
- It includes
  - letrozole
  - anastrozole
  - exemestane .
- The aromatase enzyme in fat tissue is blocked.
- The ovarian production of estrogen cannot be stopped, hence effective only in postmenopausal women who has no ovarian function, either
  - due to menopause
  - Or due to luteinizing hormone-releasing hormone analogs treatment.

  They are consumed as daily dosage pills.

The aromatase inhibitors to tamoxifen as adjuvant hormone therapy in post-menopausal women has been compared in many studies.

The risk of the recurrence on using tamoxifen alone for five years is more than usage of AI drugs, either alone or after tamoxifen.

Schedules that are helpful include:

- Tamoxifen - two to three years, followed by an aromatase inhibitor to complete the five years of treatment
- Tamoxifen for 5 years, and then an AI for 5 years
- An AI alone for 5 years

For women with early breast cancer who are in pre menopausal age,

  - At first tamoxifen is used.
  - If they attain menopause during the treatment, then an AI may be administered later
  - Other choice is shutting down the ovaries by using drugs such as a LHRH analog along with an AI.

Side effects- less serious than tamoxifen- no risk of endometrial cancer or coagulopathy. It causes muscle pain and joint stiffness.

As aromatase inhibitors remove all the estrogens in post menopausal women , they can cause thinning of bones, which in turn leads to osteoporosis.

To increase the bone strength, many women on aromatase inhibitor treatment are also given bisphosphonates or denosumab.

Ovarian ablation:

The ovarian ablation in women before menopause , resulting in the woman to attain menopause. This allows the improved working of hormone therapies and is usually used to treat the breast carcinoma with metastasis.

Permanent ovarian ablation done by surgical means- oophorectomy.

Ovarian ablation can be done with drugs such as luteinizing hormone-releasing hormone (LHRH) analogs, such as goserelin or leuprolide. These drugs act by blocking the signal sent from pituitary to the ovaries for estrogen synthesis. They can be used alone or along with other hormone drugs.

Trastuzumab:

It is a monoclonal antibody against the HER2/neu receptor. The overall survival in HER2-positive patients with metastatic breast cancer is improved. The trastuzumab and chemotherapy combination increased both the survival and response rate, when comparing with treatment with trastuzumab alone. The exact duration of trastuzumab therapy required is currently unknown. One year duration is usually accepted.

Mechanism of action:

Trastuzumab acts by binding to the domain IV of the extracellular part of the HER2/neu receptor. It causes the cell cycle to arrest inG1 phase and so there is decreased proliferation. It is also suggested that trastuzumab exerts its effect by causing downregulation of the HER2/neu leading to disruption of dimerization of receptor and also the PI3K cascade signaling is reduced. By induction of antiangiogenic factors and suppression of proangiogenic factors it suppresses angiogenesis.

Side effects:

- flu-like symptoms, nausea and diarrhea
- cardiotoxicity- it causes cardiac dysfunction in 2- 5% patients leading to congestive cardiac failure. Therefore routine echo should be done in patients receiving trastuzumab therapy. It occurs due to the downregulation of neuregulin-1 which activates the MAPK pathway and the PI3K/AKT pathway in cardiac myocytes and is essential for its survival.

Treatment for Triple negative Breast Cancer:

Triple -ve cancer has poor prognosis and are usually refractory to many therapies. Treatment involves multimodality approach such as surgery, radiotherapy, chemotherapy.

Some studies show that triple negative tumors respond better to chemotherapy when compared to receptor positive tumors.

But resistance to taxanes and anthracyclines based regimen do occur in them. For those, newer drugs are under evaluation such as

1. Eribulin- microtubule inhibitor causing mitotic blockade
2. Bevacizumab- antiangiogenesis
3. Cetuximab- against epidermal growth factor

The study literature by Desombre and Jensen demonstrated " A decrease in the ER content as a tumor progresses. PR is a surrogate marker of functional ER because PR is an estrogen-regulated gene. More than half of ER+ tumors express PR. Hence, simultaneous analysis of ER and PR gives more information regarding likely hormonal response. Some studies have reported the presence of PR as a better predictive marker of response to hormone therapy than quantitative ER. Of breast carcinomas, 55% express both ER and PR, whereas 22% do not express either ER or PR. In addition, 20% of tumors are ER+ and PR–, and 3% are ER– and PR+."

In another study conducted by Hussain Gadelkarim Ahmed, Mohammed Ali Al-Adhraei regarding correlation of ER,PR, Her2 and p53 status in Yemen women, it showed "The positive expression of different markers in all cases of ductal carcinoma: 60 (43.8%) positive for ER, 37 (27%) for PR, 42 (30.6) % for Her2/neu and 67 (48.9) % for p53. The P values of the overall expression of ER, PR, Her2/neu and P53 in cases compared with controls were 0.16, 0.01, 0.001 and 0.0001."

Fisher et al[7] found "the presence of ER is significantly associated with high nuclear grade and low histologic grades, absence of tumor necrosis, presence of marked tumor elastosis and older patient age groups."

S. B. Desai et al study[8] " 798 breast carcinomas in Indian population and found 32.6% ER positive and 46.1% PR positive. ER, PR immunoreactivity increased with advancing age and correlated with presence of elastosis. Infiltrating lobular, mucinous and mixed tumors were more frequently ER, PR positive. High grade infiltrating duct carcinoma , pure comedo DCIS and medullary carcinomas were predominantly ER, PR negative. The presence of necrosis and lymphovascular invasion showed an inverse relationship with ER and PR reactivity."

Lakmini K. B. Mudduwa[9] "studied 151 breast carcinomas for ER , PR status by using quick score. Quick score for ER was 0 in 54.3% and for PR was 0 in 51.7%. the Nottingham grade, the mitotic count and the Nottingham Prognostic Index had a significant inverse relationship with quick score for hormone receptor status."

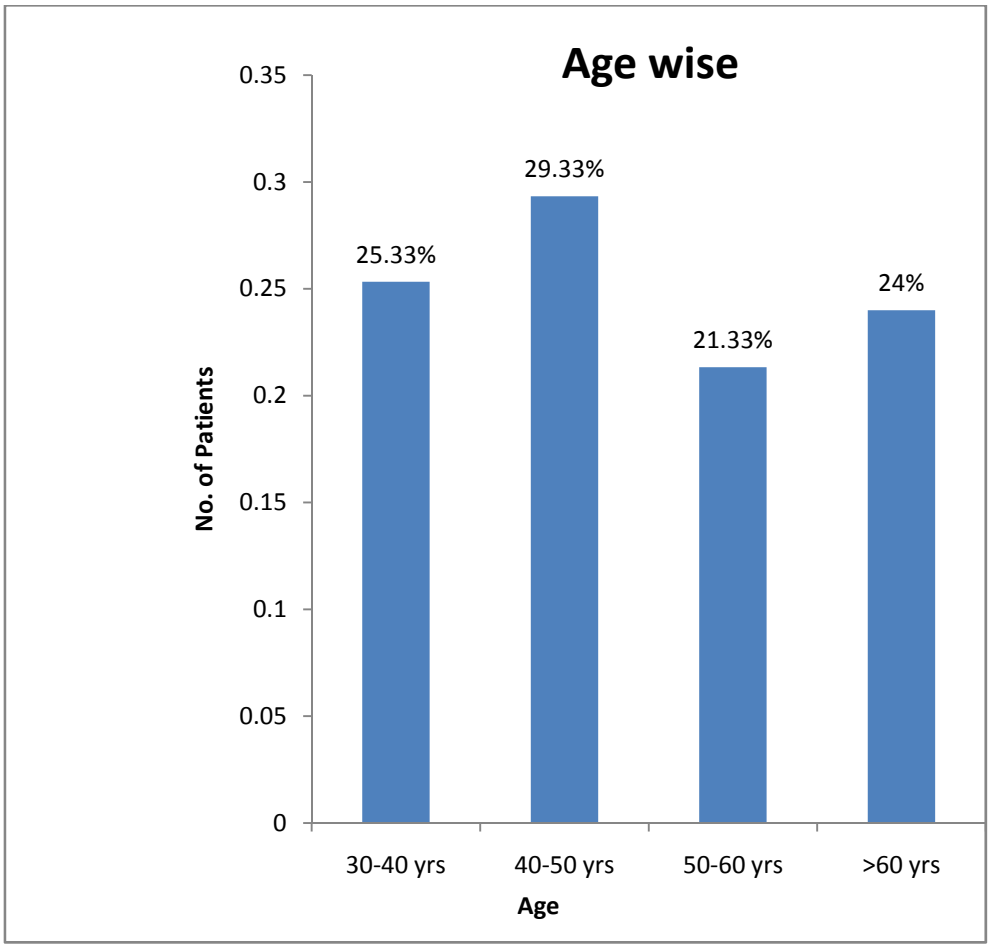
Onitilo et al study[13] "1134 cases of invasive breast carcinomas, it was observed that cases with ER,PR positive and Her2 neu negative subtype were more likely be older, have early stage breast carcinoma, present with smaller tumor and have a well/moderately differentiated histological grade. They were less likely be lymphnode positive, have a lobular phenotype and be treated with chemotherapy."

Bhargava et al[10] studied "cytological nuclear grading of breast carcinoma and its correlation with ER/PR expression in 30 cases of carcinoma breast. On correlating Robinson's nuclear grading with ER and PR status there was significant correlation between ER, PR positivity and lower nuclear grades."

Studies by Ruibal et al[11] and Thike et al[12] "showed an association of the histological tumor grade with the ER/PR content. A transition from lower to higher histological grades was accomplished by a decrease in ER/PR content."

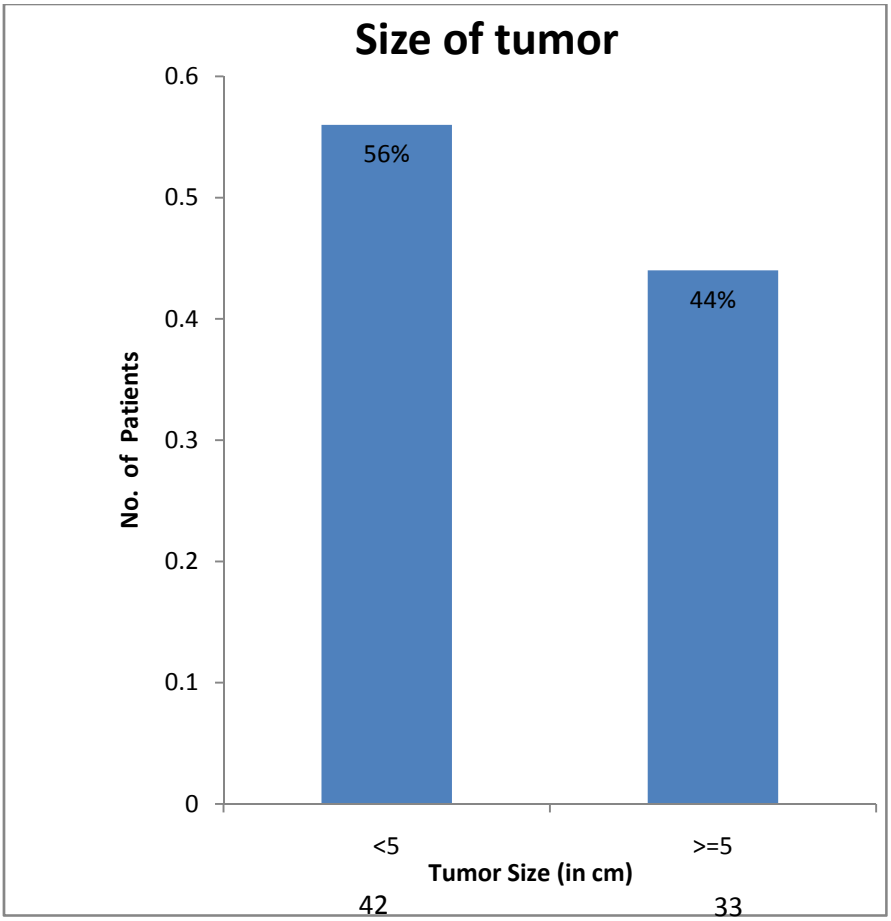
Observation and Results

OBSERVATION AND RESULTS

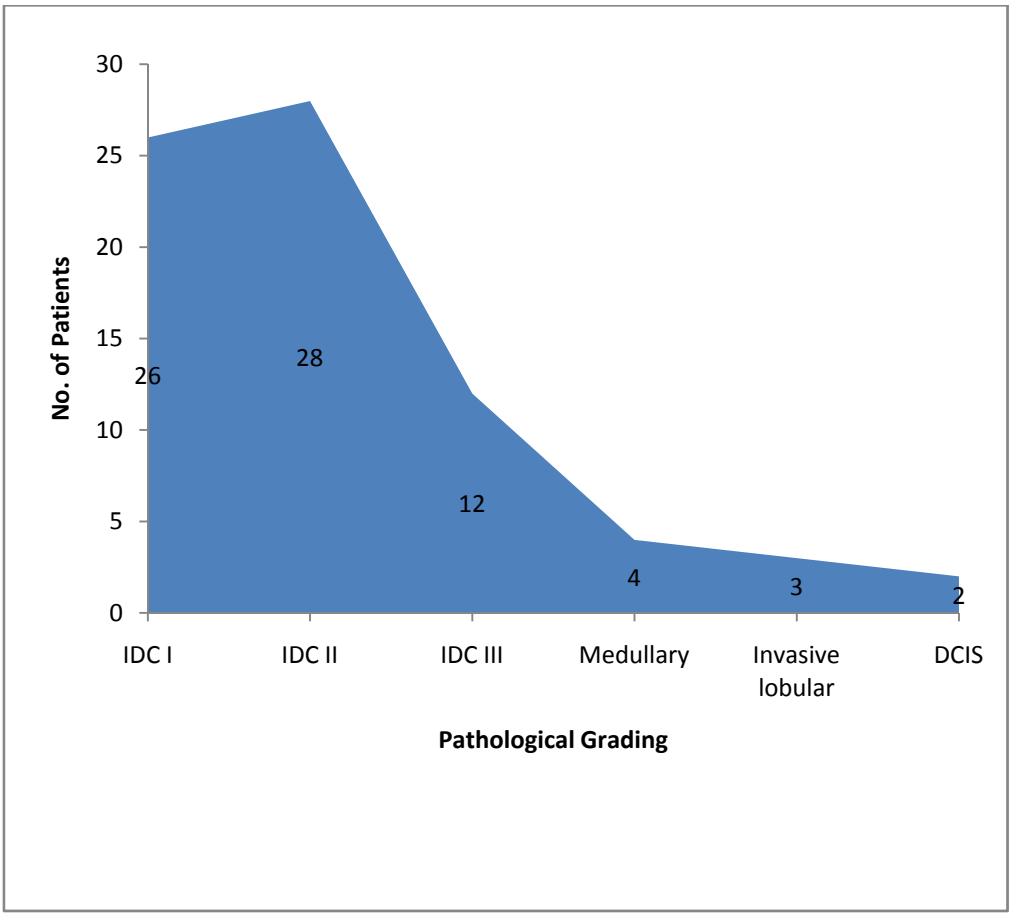


In this study, a total of 75 patients were studied starting from the age groups above 30. Most of them were between 40 and 50 years. Second most common was in younger age less than 40 years.

Most of the patients came under the age group 40- 50 years about 29.33%. The least was in the 50- 60 years age of about 21.33%



In our study group, 42 patients had a tumor of size less than 5 cm which is about 56% of the whole group. 33 patients had a tumor greater than or equal to 5cm in size which constitutes 44% of the study sample.



In this study which included breast cancers of different histological types and grade

IDC I- 26 patients

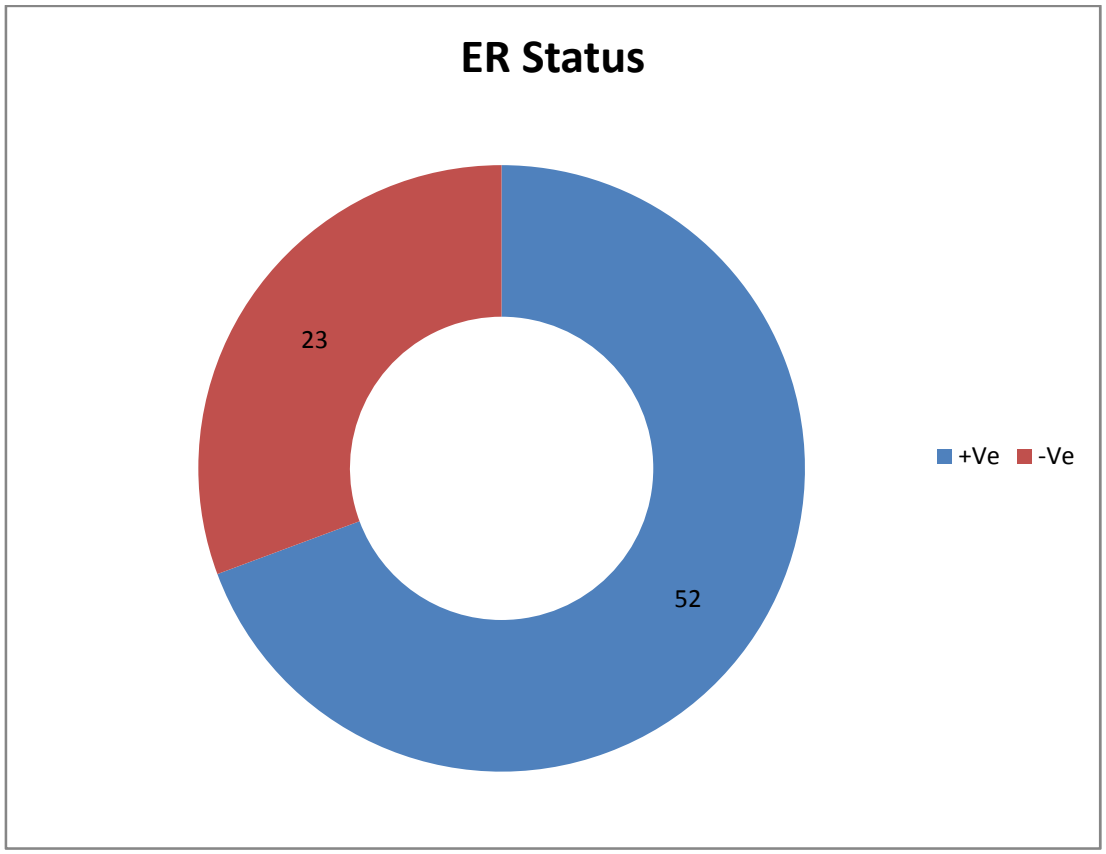
IDC II- 28 patients

IDC III- 12 patients

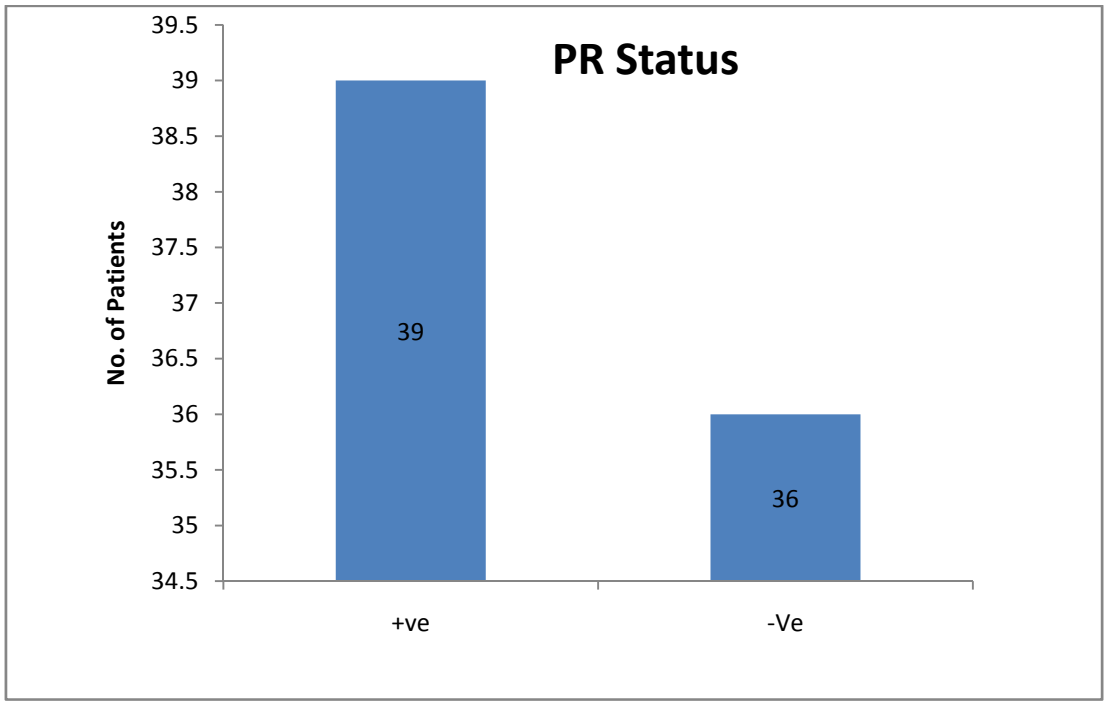
Medullary carcinoma- 4

Invasive lobular carcinoma- 3

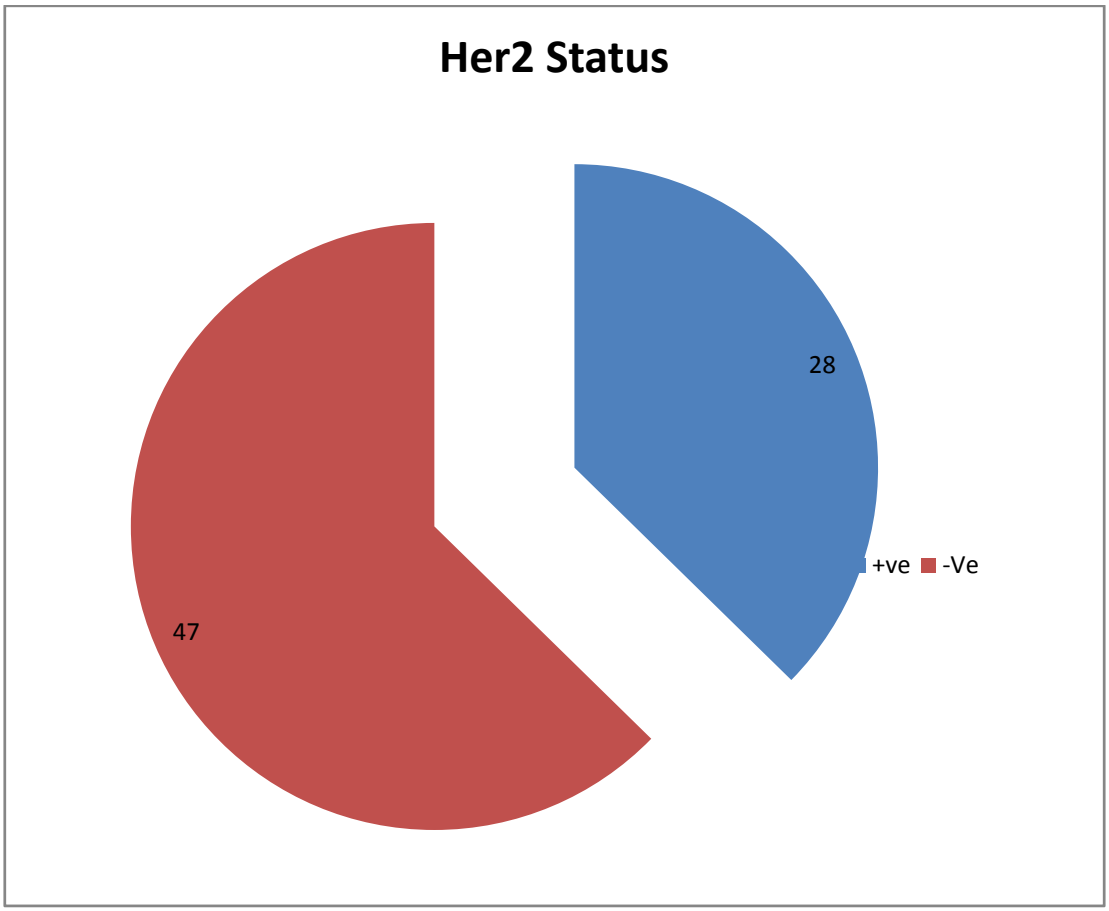
Ductal carcinoma insitu- 2



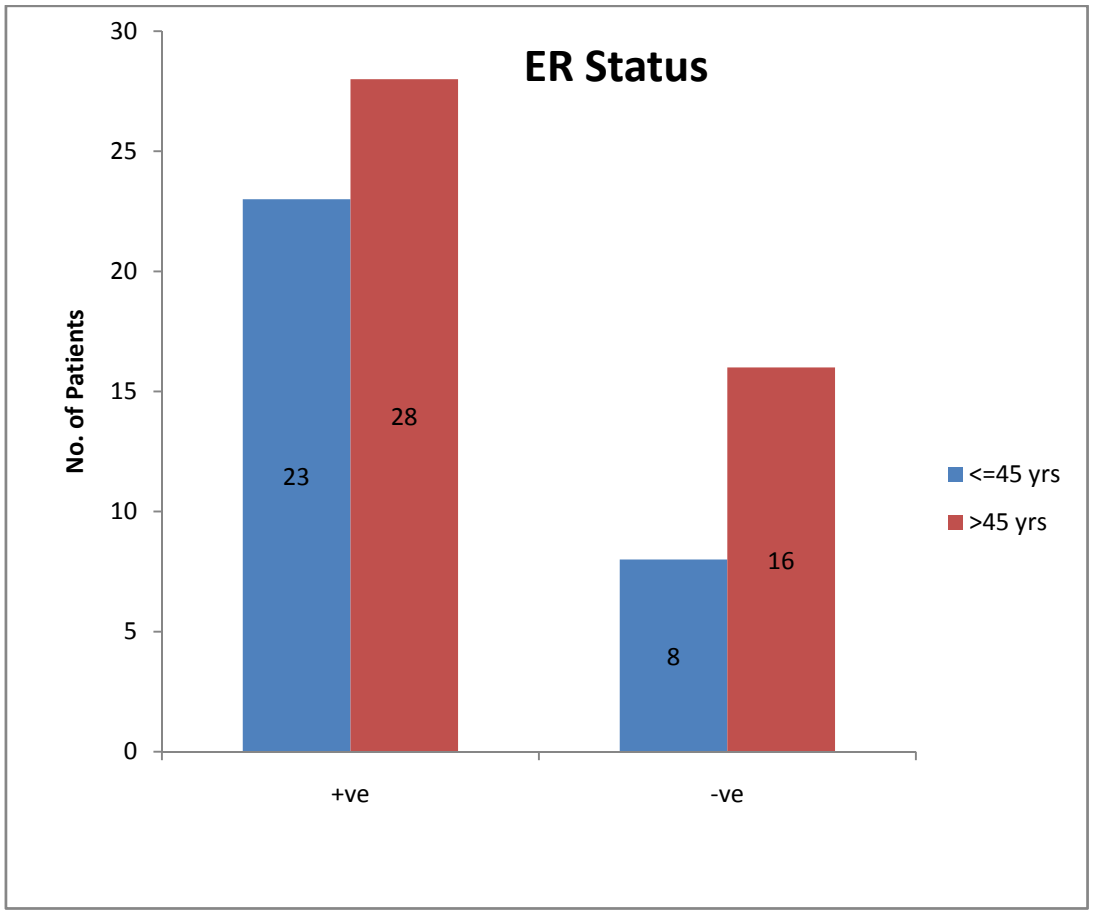
Out of 75 patients, 52 patients (69.33%) were positive for estrogen receptor and 23 (30.66%) were negative.



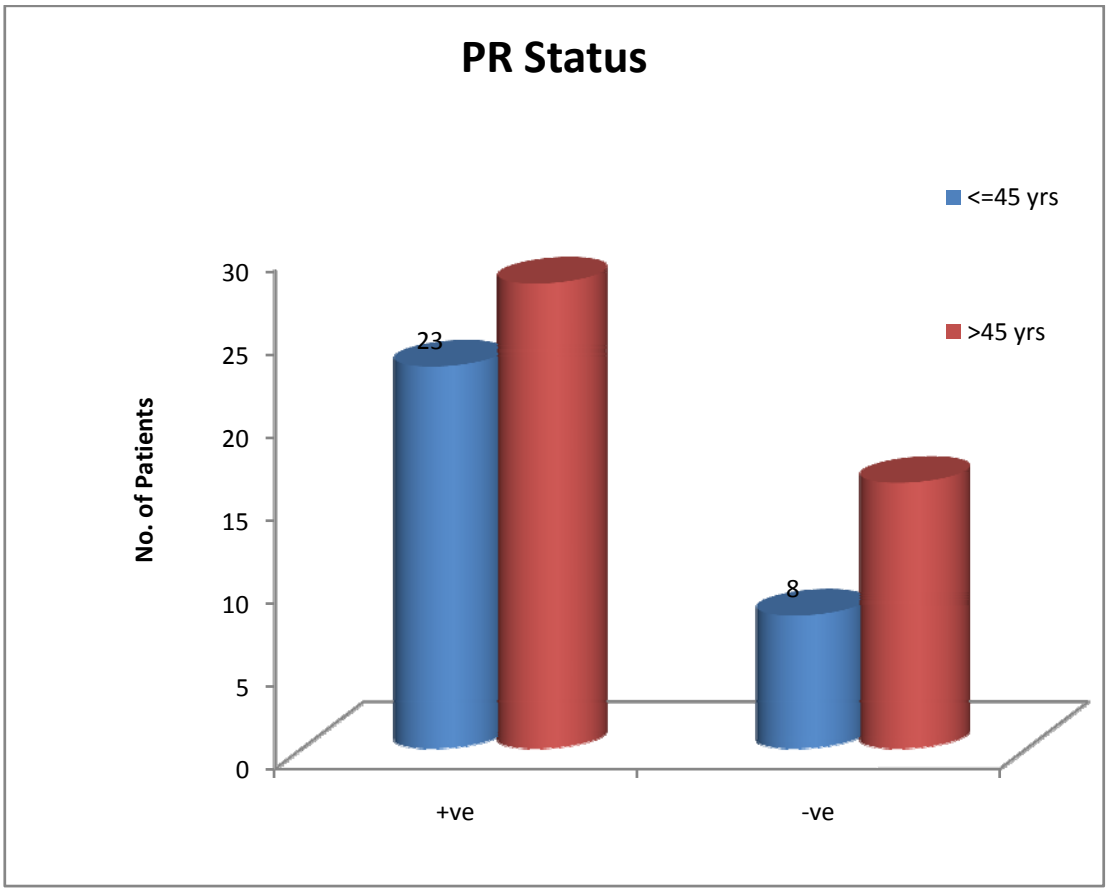
39 patients (52%) were progesterone receptor positive and 36 (48%) were progesterone receptor negative.



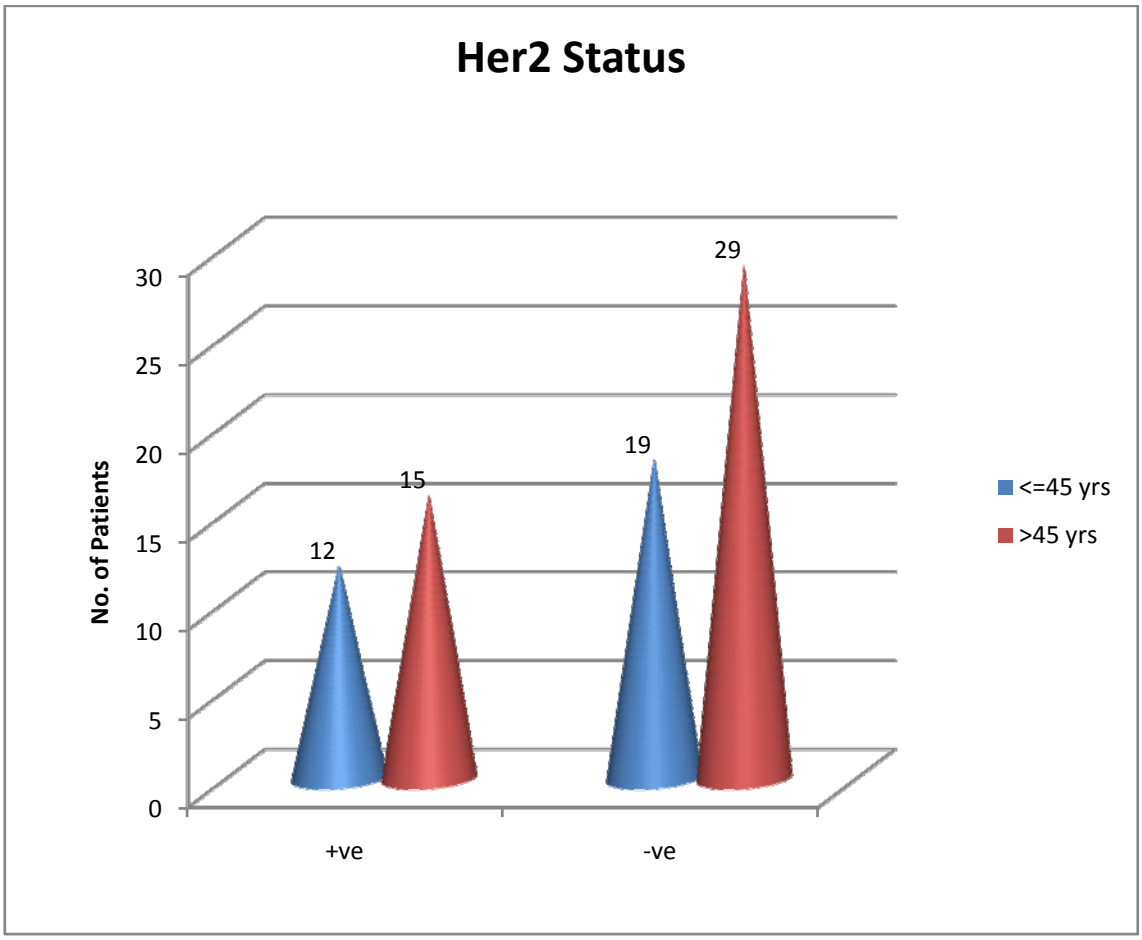
Here 28 (37.33%) patients had Her2 receptor positive and 47 (62.66%) were negative.



In patients under 45 years of age (total 31), 23 patients (74.19%) were ER positive and 8 (25.81%) were negative. Above 45 years of age (total 44), 28 patients (63.63%) were ER positive and 16 (36.36%) were negative.

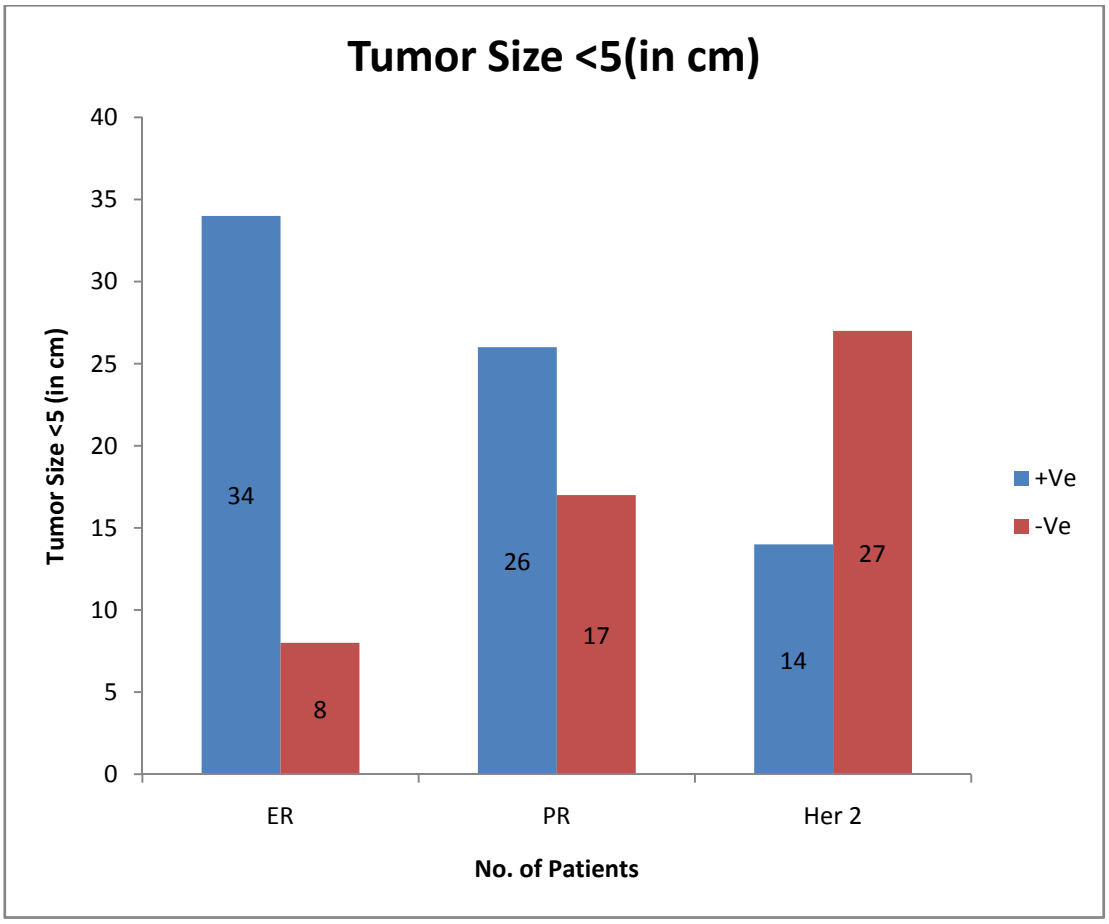


In estimation of PR receptors, under 45 years 23 patients (74.19%) were PR positive and 8 (25.81%) were negative. Above 45 years of age 28 (63.63%) patients were PR positive and 16 (36.36%) were negative.



<45 years- 12 patients (39%) positive ; 19 (61%) negative

>45 years- 15 patients (34%) positive ; 29 (66%) negative



In tumors less than 5 cm in size

ER positive- 34 patients

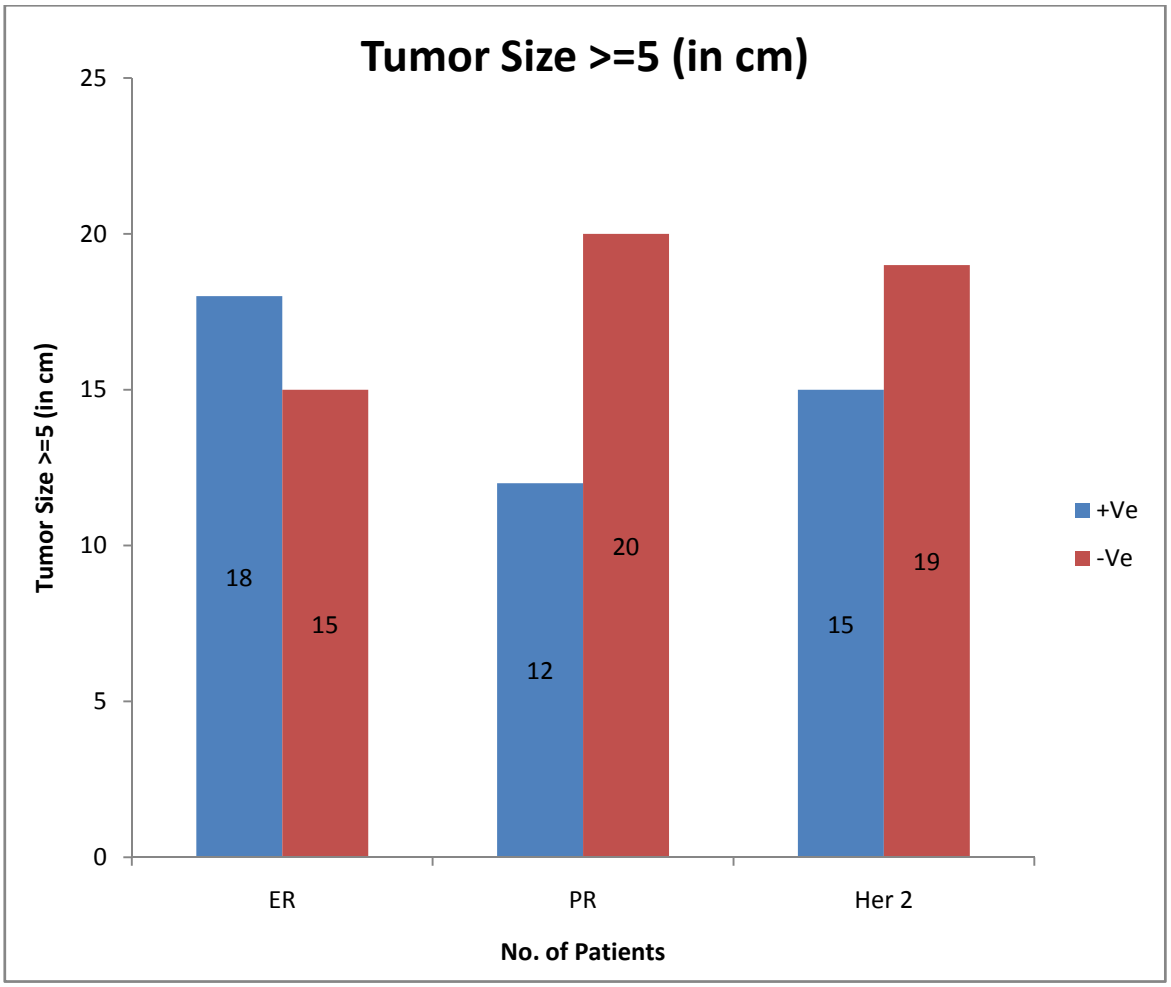
ER negative- 8 patients

PR positive- 26 patients

PR negative- 17 patients

Her2 positive- 14 patients

Her2 negative- 27 patients



In tumors more than or equal to 5 cm in size

ER positive- 18 patients

ER negative- 15 patients

PR positive- 12 patients

PR negative- 20 patients

Her2 positive- 15 patients

Her2 negative- 19 patients

Summary

SUMMARY

Breast cancer is one of the most common cancers among women of all age groups. In recent years the there is an increase in the incidence of breast cancer due to the lifestyle modifications, and increase in screening programs which help to detect them at an early stage. Breast cancer treatment involves a multidisciplinary approach. Hormone therapy is one among the treatment modality. Estrogen, progesterone and Her2 neu receptor status estimation is very crucial at present in order to predict the tumor response to the hormonal therapy and also to assess the prognosis of the cancer.

Conclusion

CONCLUSION

In my study a total of 75 female patients with breast cancer in my institute were studied. the incidence of ER, PR, Her2 neu receptors among them correlating with age, tumor size, histological type and the pathological grading was evaluated. 52 patients (69.33%) were positive for estrogen receptor and 23 (30.66%) were negative. 39 patients (52%) were progesterone receptor positive and 36 (48%) were progesterone receptor negative. 28 (37.33%) patients had Her 2 receptor positive and 47 (62.66%) were negative.

Most of the tumors in women above45 years of age were hormone receptor positive. In women younger than 45 years both positive and negative were nearly equal. Similar results were observed in tumors less than 5cm where positivity predominated and more than 5 cm where both positive and negative were utmost equal. Her 2 was more negative in most of the patients of our study irrespective of age and tumor size.

These results were comparable with the previous studies and thus reinforce the usefulness of estimation of the receptor status for treatment purpose in breast carcinoma.

All patients with hormone receptor positivity were started with tamoxifen 10 mg bd for a total duration of 5 years and their compliance is good till date with minimal side effects.

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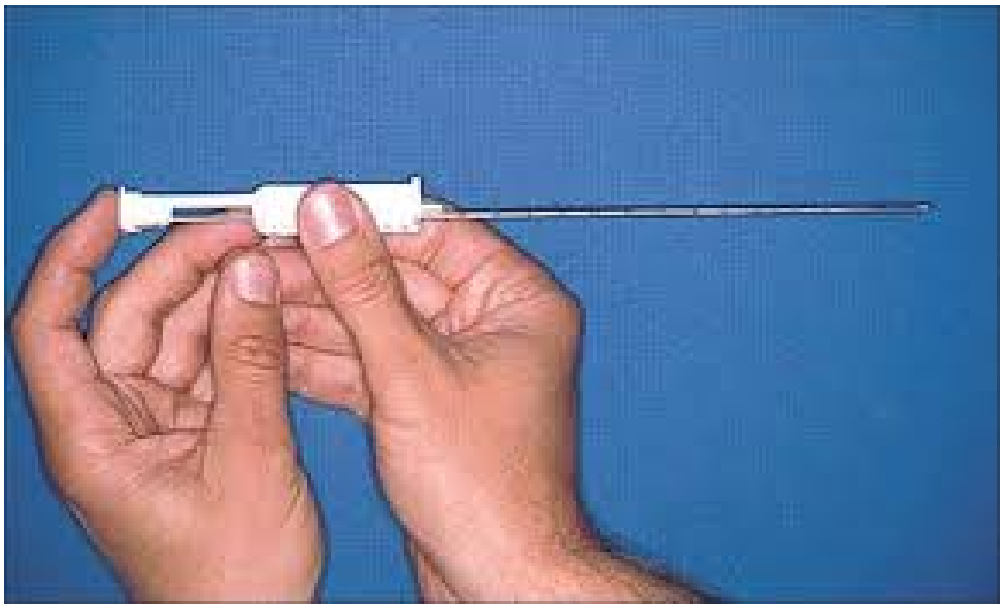
Annexures

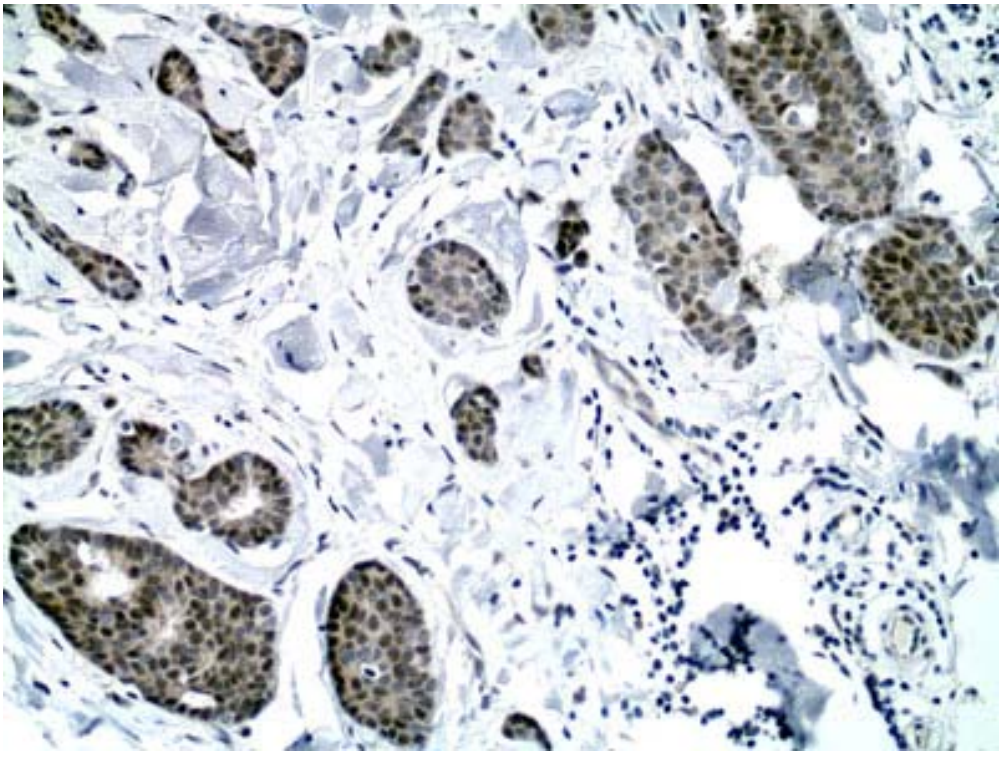
ANNEXURE I

PHOTOS

Trucut Biopsy Needle



Estrogen receptor positive



ANNEXURE II

PROFORMA

1. Name:
2. Age:
3. Sex:
4. Inpatient no:
5. Duration of illness:
6. Size of tumor:
7. Specimen: trucut biopsy/ mastectomy
8. FNAC / Biopsy report:
9. Grade of the tumor:
10. Estrogen receptor:
11. Progesterone receptor:
12. Her2 neu receptor:

ANNEXURE III

CONSENT FORM

I exercising my free power of choice, hereby give my full free and voluntary consent for myself to be a subject of the study “Clinical study of hormone receptor status in carcinoma breast”.

I have been informed to my satisfaction by attending surgeon Dr. …… the purpose of the study, the clinical and pathological investigations that are to be carried out and the nature and consequences of the surgery, anaesthesia and the likely complications in my own language.

I am aware of my right to not to opt for this study without having to give reasons for doing so.

Signature of the surgeon:`

Date:

Signature of the patient:

Date:

ANNEXURE IV

MASTER CHART

SL. No	Name	Age	Sex	Tumor Size (in cm)	Pathological Grading	ER Status	PR Status	Her 2 Status
1	Chinnathai	70	F	3 * 3* 2	IDC NOS TYPE II	-ve	1+	+ve
2	Annaselvi	65	F	5 * 3 * 3	IDC NOS TYPE I	2+	-ve	1+ve
3	Mariammal	35	F	4* 2 * 3	IDC NOS type I	3 +	2+	-ve
4	Mydeenmeeral	53	F	5 * 2 * 2	IDC NOS type grade II	-ve	-ve	-ve
5	Ulagamayee	42	F	6 * 3 * 4	IDC medullary type	-ve	-ve	-ve
6	Mariammal	40	F	4 * 3 * 1	IDC NOS TYPE II	+	+	-ve
7	Valliammal	65	F	7 * 4 * 2	IDC NOS TYPE III	-ve	+	-ve
8	Puthiyal	65	F	6 * 5 * 2	IDC NOS TYPE III	-ve	-ve	-ve
9	Natchiyar	60	F	4 * 4 * 3	IDC NOS TYPE II	-ve	-ve	-ve
10	Latha	39	F	2 * 2 * 1	Pagets disease	2 +	-ve	-ve
11	Annalakshmi	58	F	4 * 3 * 2	IDC NOS TYPE I ductal carcinoma insitu	4 +	2 +	-ve
12	Thangammal	70	F	7 * 4 * 3	IDC NOS TYPE I ductal carcinoma insitu	4 +	2 +	-ve
13	Annal	62	F	6 * 4 * 2	IDC NOS TYPE II	-ve	-ve	2+
14	Shanthi	36	F	4 * 4 * 2	IDC NOS TYPE II	2 +	-ve	-ve
15	Mariammal	40	F	3 * 3 * 2	IDC NOS TYPE II	2 +	-ve	1+ve
16	Shyamala	39	F	4 *3 * 2	IDC NOS TYPE III	-ve	-ve	-ve
17	Lakshmi	35	F	2 * 2 * 1	IDC NOS TYPE I	1+	1+	1+
18	Sudha	48	F	5 * 4 * 2	IDC NOS TYPE II	-ve	-ve	1+
19	Vijayalakshmi	45	F	4 * 2 * 2	IDC NOS TYPE I	2+	+	1+
20	Mallika	40	F	4 * 3 * 2	IDC NOS TYPE I	3 +	3 +	-ve
21	Latha	41	F	2 * 1 * 1	IDC NOS TYPE II	-ve	-ve	-ve
22	Rasammal	49	F	5 * 3 * 2	IDC NOS TYPE II	3 +	3 +	-ve
23	Chellamal	63	F	6 * 3 * 3	IDC NOS TYPE III	-ve	-ve	1+
24	Thamaraiselvi	48	F	5 * 3 * 2	IDC NOS TYPE II	1 +	2 +	2+

SL. No	Name	Age	Sex	Tumor Size (in cm)	Pathological Grading	ER Status	PR Status	Her 2 Status
25	Rasool beevi	70	F	7 * 4 * 2	IDC NOS TYPE I	2+	1+	1+
26	Piramu	59	F	6 * 3 * 2	IDC NOS TYPE I	4 +	3 +	-ve
27	Masanam	31	F	2 * 1 * 2	IDC NOS TYPE II	3 +	-ve	-ve
28	Leelavathy	36	F	3 * 2 * 2	IDC NOS TYPE I	4 +	3 +	-ve
29	Natchiyar	60	F	4 * 4 * 1	IDC NOS TYPE I	2 +	3 +	-ve
30	Maideen Nisha	45	F	4 * 2 * 3	IDC NOS TYPE III	-ve	-ve	4+
31	Ponselvi	53	F	3 * 2 * 2	IDC with comedocarcinoma	2 +	-ve	3+
32	Lakshmi	35	F	5 * 3 * 3	IDC NOS TYPE II	2 +	-ve	-ve
33	Esakkiammal	47	F	3 * 3 * 3	IDC NOS TYPE III	-ve	-ve	2+
34	Valliamal	60	F	4 * 2 * 3	IDC NOS TYPE II	2 +	-ve	2+
35	Gandhimathi	80	F	7 * 5 * 2	IDC with mucinous areas	2 +	-ve	3+
36	Subbulakshmi	52	F	4 * 2 * 2	IDC NOS TYPE I	2 +	-ve	2+
37	Maharaj	53	F	5 * 3 * 3	IDC NOS TYPE II	-ve	-ve	-ve
38	Ramalatha	64	F	6 * 3 * 3	IDC NOS TYPE II	-ve	-ve	1+
39	Murugathal	58	F	4 * 2 * 1	Invasive lobular carcinoma	3 +	3 +	-ve
40	Esakkiammal	47	F	5 * 3 * 3	IDC NOS TYPE I	2+	2+	-ve
41	Muthulakshmi	47	F	2 * 2 * 1	IDC atypical medullary type	4 +	2 +	-ve
42	Mariammal	35	F	3 * 1 * 1	IDC NOS TYPE II	2 +	-ve	3 +
43	Ponselvi	45	F	4 * 2 * 1	IDC with comedocarcinoma	2+	1+	-ve
44	Chandra	45	F	5 * 3 * 3	IDC NOS TYPE II	2 +	-ve	-ve
45	Papa	55	F	7 * 4 * 3	IDC NOS TYPE I	2 +	2 +	-ve
46	Iyyammal	45	F	5 * 3 * 1	IDC NOS TYPE III	-ve	-ve	+
47	Meharaj	83	F	4 * 4 * 2	IDC NOS TYPE I	3 +	3 +	-ve
48	Annakaamal	65	F	3 * 4 * 2	IDC NOS TYPE III	-ve	-ve	-ve

SL. No	Name	Age	Sex	Tumor Size (in cm)	Pathological Grading	ER Status	PR Status	Her 2 Status
49	Bhuvaneshwari	32	F	5 * 5 * 2	IDC NOS TYPE II	2 +	-ve	2 +
50	Rajalakshmi	43	F	2 * 2 * 1	IDC NOS TYPE III	2 +	-ve	2 +
51	Chellathai	62	F	4 * 2 * 2	IDC NOS TYPE I	1 +	-ve	-ve
52	Sundari	60	F	3 * 2 * 2	IDC NOS TYPE I	3 +	3 +	1 +
53	Chinnathai	65	F	6 * 4 * 3	IDC NOS TYPE II	-ve	1 +	-ve
54	Pushpam	38	F	3 * 2 * 2	IDC NOS TYPE I	2 +	3 +	-ve
55	Ramu	37	F	4 * 2 * 2	IDC NOS TYPE II	+	+	+
56	Jebam ani	46	F	3 * 2 * 1	IDC NOS TYPE I	2 +	1 +	-ve
			F	4 * 3 *2	IDC NOS TYPE II	2 +	1 +	-ve
58	Ramu	45	F	2 * 1 * 1	IDC NOS TYPE I	3 +	2 +	+
59	Marthal	54	F	3 * 3 * 1	IDC NOS TYPE II	3 +	3 +	-ve
60	Rani	44	F	6 * 4 * 2	Ductal/ lobular carcinoma	-ve	-ve	-ve
61	Esakiammal	27	F	5 * 3 * 2	IDC NOS TYPE II	1 +	-ve	-ve
62	Sundari	47	F	4 * 4 * 1	IDC cribriform	+	+	-ve
63	Rathinam	70	F	6 * 4 * 2	IDC NOS TYPE III with DCIS	-ve	-ve	-ve
64	Raajam	61	F	7 * 5 * 2	IDC with medullary type	-ve	-ve	-ve
65	Gandhimathi	31	F	5 * 2 * 1	IDC NOS TYPE II	2 +	-ve	-ve
66	Maheshwari	48	F	4* 3* 3	IDC NOS TYPE II	1+	1+	-ve
67	Annalakshmi	63	F	6* 4* 2	IDC NOS TYPE III	-ve	-ve	1+
68	Kanagavalli	52	F	3* 3* 2	Ductal carcinoma insitu	2+	3+	-ve
69	Alagammal	37	F	5 * 2 * 2	IDC with medullary type	1+	1+	1+
70	Ganga	57	F	4 * 2 * 2	Invasive lobular Carcinoma	2+	2+	-ve
71	Natchiyar	66	F	3 * 2 * 2	IDC NOS TYPE I	2+	1+	-ve
72	Amuthavalli	39	F	4 * 3 * 2	IDC NOS TYPE III	-ve	1+	1+

SL. No	Name	Age	Sex	Tumor Size (in cm)	Pathological Grading	ER Status	PR Status	Her 2 Status
73	Mariyam	49	F	6 * 3 * 3	Ductal carcinoma insitu	3+	2+	-ve
74	Mydeen beevi	54	F	5 * 3 * 2	IDC NOS TYPE II	2+	2+	1+
75	Karpagam	45	F	5 * 4 * 3	IDC NOS TYPE II	1+	1+	-ve

ANNEXURE V

KEY TO MASTER CHART

ER	**–**	estrogen receptor
PR	**–**	progesterone receptor
HER2	**–**	human epidermal growth factor receptor
+ve	**–**	positive
-ve	**–**	negative
IDC	**–**	invasive ductal carcinoma
DCIS	**–**	ductal carcinoma insitu
NOS	**–**	no other specified type